Published in final edited form as:

Arthritis Rheumatol. 2018 February ; 70(2): 212–221. doi:10.1002/art.40325.

Knee Alignment is Quantitatively Related to Periarticular Bone Morphometry and Density, Especially in those with Osteoarthritis

Grace H. Lo, MD, MSc¹, Mehveen Merchant, MD², Jeffrey B. Driban, PhD³, Jeffrey Duryea, PhD⁴, Lori Lyn Price, MAS, MLA⁵, Charles B. Eaton, MD, MS⁶, and Timothy E. McAlindon, DM Soton⁷

¹Department of Medicine, Baylor College of Medicine, Houston, TX; Medical Care Line and Research Care Line, Houston VA HSR&D Center for Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey Medical Center, Houston, TX, USA

²Department of Medicine, Nova Scotia Health Authority, Dalhousie University, Halifax, Nova Scotia, Canada

³Division of Rheumatology, Department of Medicine, Tufts Medical Center, Boston, MA, USA

⁴Department of Radiology, Brigham and Women's Hospital, Boston, MA, USA

⁵The Institute for Clinical Research and Health Policy Studies, Tufts Medical Center; Tufts Clinical and Translational Science Institute, Tufts University, Boston, MA, USA

⁶Department of Family Medicine and Epidemiology, Memorial Hospital of Rhode Island and Alpert Medical School of Brown University, Pawtucket, RI, USA

⁷Division of Rheumatology, Department of Medicine, Boston, MA, USA

Abstract

Objective—Static alignment influences knee loading and predicts osteoarthritis (OA) progression. Periarticular bone is important in dispersing forces across the knee. And there is substantial evidence for molecular crosstalk between cartilage and subchondral bone. Our objective was to evaluate the relationship of periarticular trabecular morphology and bone mineral density (BMD) with knee alignment.

Methods—This was a cross-sectional analysis of Osteoarthritis Initiative (OAI) Bone Ancillary Study participants. Dual-energy x-ray absorptiometry (DXA) measured tibial periarticular BMD (paBMD). Knee trabecular magnetic resonance images (MRIs) were used to calculate apparent bone volume fraction, trabecular number, spacing and thickness (aBVF, aTb.N, aTb.Sp, and aTb.Th). Static alignment, hip-knee-ankle (HKA) angle, was measured on long limb films.

Results—436 participants, mean age 65.4 years (s.d. 9.2), 46% female, mean body mass index 29.6 kg/m² (s.d. 4.6); 71% had OA. Correlations between HKA and medial:lateral paBMD, medial paBMD, aBVF, aTb.N, aTb.Th, and aTb.Sp were −0.63, −0.34, −0.29, −0.32, −0.22, 0.30

* Address correspondence and reprint requests to Grace H. Lo, MD MSc, Baylor College of Medicine, Houston, TX, 1 Baylor Plaza, BCM-285, Houston, TX 77030; ghlo@bcm.edu; Telephone number: 713-798-7313; Fax number: 713-798-5780.

respectively (more varus alignment was associated with higher medial:lateral paBMD, medial paBMD, aBVF, aTb.N, and aTb.Th and lower aTb.Sp). In OA knees, the results were more pronounced. In non-OA knees, the most consistent association was with medial:lateral paBMD.

Conclusion—Static alignment was associated with medial:lateral paBMD in all knees; and with medial paBMD and trabecular morphometry in OA knees only. Aberrant knee loading may lead to increased relative subchondral bone density, partly related to higher bone volume fraction, number of thicker trabeculae with smaller inter-trabecular spacing. Knee DXA may be a useful early biomarker for knee OA.

Introduction

Knee osteoarthritis (OA) is a substantial public health problem affecting an estimated 30.8 million people in the United States (1). This is the most common type of arthritis, a common chronic complaint in the outpatient setting (2), and the source of substantial disability (2), yet few effective treatments currently exist, including nonsteroidal anti-inflammatory medications, physical therapy, and ultimately total knee replacement for patients with the most severe disease. Better understanding the natural history of this disease may play a critical role in identifying novel effective therapies.

There is substantial evidence for crosstalk between cartilage and subchondral bone at a molecular level (3, 4). Although often characterized as a disorder of articular cartilage, prominent among the protean pathophysiological manifestations of knee OA are the presence of malalignment and changes in the peri-articular bone. Furthermore, biomechanical studies have shown that much of the load dispersion across a knee occurs within the peri-articular bone, up to 50% compared to only ~3% by hyaline cartilage (5). Static alignment influences load distribution in the knee joint and is predictive of disease progression in the compartment in which load is increased (6, 7).

Measures of periarticular bone in OA can be obtained by dual-energy x-ray absorptiometry (DXA) of peri-articular bone mineral density (paBMD) and magnetic resonance imaging (MRI)-based trabecular morphometry (8–20). These measures are also strongly associated with the presence of knee OA. Knee OA is associated with a higher DXA measured tibial paBMD, trabecular bone volume fraction, trabecular number, and thickness, but lower trabecular spacing (13–15, 18, 21).

Because static alignment affects load distribution and is a potent predictor of knee OA progression and aberrations in periarticular bone are prominent in knee OA, we hypothesized that static alignment is associated with periarticular bone measured by DXA (paBMD) and MRI (bone volume fraction, trabecular number, and thickness, trabecular spacing). Further, we expected this relationship to be present in those with and without radiographic evidence of knee OA as we anticipated that static alignment influences periarticular bone changes antedating the development of radiographic OA. To address this question, we performed a knee-based cross-sectional study of participants of the Osteoarthritis Initiative who had periarticular bone and static alignment measures.

Materials and Methods

Overall Study Design

This was a knee-based cross-sectional study nested within two ancillary studies to the Osteoarthritis Initiative, including only members of the progression cohort who had static alignment measures in addition to DXA measures of paBMD and MRI assessed trabecular morphometry.

Parent Study Design

The Osteoarthritis Initiative (OAI) is a multi-center observational study focused on identifying biomarkers of knee OA (22). Four clinical centers participated in this study: The University of Maryland School of Medicine, The Ohio State University, University of Pittsburgh, and Memorial Hospital of Rhode Island. The coordinating center was the University of California, San Francisco. OAI participants were males and females, ages 45–79 years, from all ethnic groups. The progression subcohort included those with at least one knee with symptomatic tibiofemoral knee OA in a native knee.

As the OAI was designed to address multiple scientific questions, annual standard knee radiographs were obtained as part of the parent study. Static alignment and periarticular bone measures were not part of the original protocol, and were not obtained on all participants at the same visits. Long-limb films, funded by one ancillary study, were used to measure mechanical alignment were obtained mostly at the 12 month visit (86%). However, if time did not permit, then these films were obtained at the subsequent 24- or 36- month visits. In a separate ancillary study, knee DXAs and trabecular MRI were obtained only from participants in the OAI progression subcohort seen from August 8, 2007 to April 3, 2009 who attended their 30- or 36- month visits and were willing to have additional knee DXA and trabecular MRI sequences. Those with contraindications to MRI and/or bilateral knee replacements at the time of the OAI 30- or 36-month visit were excluded. Those who had 30- or 36- month visit knee DXAs and trabecular knee MRIs additionally had 48- month follow up exams with knee DXAs and MRIs.

To align the time points of data which were evaluated, only participants with OAI 48- month visit data including: knee DXA, trabecular morphometry, and standard radiographs were included in these analyses. Additionally, at least one measure of mechanical alignment obtained from long limb films at any time point was also required.

Standing long limb films

The gold standard method of measuring static alignment is standing long-limb films that measure the hip-knee-ankle (HKA) angle. These films included the hip and tibiotalar joints. Participants were asked to stand with the tibial tubercle facing forward. The distance between the x-ray beam and the participant was 2.4m. Settings of 100 – 300mA/s and 80–90 kV were used to optimize the film for limb size and tissue characteristics. These films were taken of bilateral lower extremities. HKA measurements represent the angle at the intersection of two lines (1) the line connecting the femoral head and intercondylar notch centers and (2) the line connecting the ankle talar surface center and tibial interspinous

sulcus base. We used publicly-released centralized readings, supervised by Dr. Derek Cooke (OASYS Inc). Inter-reader reproducibility was high (intra-class correlation coefficient = 0.99)(23). By convention, negative values were varus, positive values were valgus.(23)

Knee Radiographs

Weight-bearing, bilateral, fixed-flexion, posterior-anterior radiographs of the knees were obtained at the OAI 48 month visit. These images were measured for anatomic axis alignment, the femoral tibial angle (FTA), using proprietary software, supervised by Dr. Jeff Duryea; these measures were downloaded from a publicly-released dataset (24). Based on recommendations by Iranpour-Boroujeni et al, we applied a sex-specific adjustment to the FTA to more closely reflect HKA (25). Additionally, these images were centrally scored for overall radiographic severity using Kellgren-Lawrence grades (0 – 4) and medial JSN grades (0 – 3) using the OARSI Atlas (27), readings which were funded by the parent OAI study and publicly-released. The reliability for these readings (read-reread) was good (weighted kappa [intra-rater reliability] = 0.70 – 0.78) (28).

MRI acquisition

Using a 3T Siemens Trio MRI scanner, trabecular sequences were obtained at the OAI 48-month visit on one knee, the right knee unless there was a contraindication, a decision made out of convenience for the participants of the parent study. The parameters for these sequences were: coronal-oblique 3D FISP, 72 slices, 1 mm slice thickness, with in-plane spatial resolution of 0.23 mm X 0.23 mm. It had a 12 cm imaging field-of-view, 512 X 512 matrix, TE 4.92 msec (fat-water in-phase), TR 20 msec, flip angle 50° phase right/left, no partial Fourier (29).

Measurement of MRI trabecular morphometry

Full details for measuring trabecular morphometry using a proprietary software have been published (29–31). One reader analyzed all the images. A standardized signal intensity threshold was applied to create a bone mask. A signal threshold was selected after application of twenty 0.7mm diameter circular regions of interest (ROI) in the cortical bone of the medial and lateral femoral condyles. A rectangular ROI was then placed on 20 consecutive coronal slices, central to the medial tibia. The standardized rectangular ROI had a height of 3.75 mm and the width of 14–17 mm, varying with the size of the tibial plateau. The ROI was placed adjacent to the articular cartilage (figure 1A). The 20 ROIs were then analyzed providing measurements of apparent total bone volume fraction (aBVf), apparent trabecular thickness (aTb.Th), apparent trabecular number (aTb.N), and apparent trabecular spacing (aTb.Sp). The aBVf (apparent bone volume/total volume) was calculated as the percent of pixels comprising the void in the bone signal over the total number of pixels in the ROI. The aTb.Th was calculated by obtaining the mean of the intercept length of all angles through a given image in millimeters. The aTb.N was calculated by dividing aBVf by aTb.Th. The aTb.Sp was calculated by $(1/aTb.N) - aTb.Th$. For each trabecular morphometry parameter, an average was obtained of each knee's 20 ROIs. The intra-rater (measurement-remeasurement) reliability had the following intra-class correlations (ICC): 0.97 [95%

confidence interval (CI) 0.91–0.99] for aBVF, 0.98 (95% CI 0.92–0.99 for aTb.Th, 0.92 (95% CI 0.73–0.98) for aTb.N, and 0.77 (95% CI 0.38–0.93) for aTb.Sp (31).

DXA acquisition

At the OAI 48-month visit, bilateral knees were imaged unless contraindicated. Each of the four clinical sites had identical DXA scanners (Lunar Prodigy Advance scanner, GE Lunar Cop., Madison WI, USA). Details on obtaining the tibial DXA scans have been published (13). In brief, the lower extremity was placed with the tibia perpendicular to the x-ray beam in a neutral position and with the knee slightly flexed with the assistance of knee and foot positioners.

DXA analysis

Full details of the tibial plateau paBMD measurements have been published (13). The tibial ROIs had a height of 10 mm and the width of the medial and lateral ROIs each were half the width of the tibial plateau (figure 1B). The superior portion of the rectangle was aligned parallel to the superior aspect of the medial joint surface of the tibia. We calculated the medial:lateral periarticular BMD (medial:lateral paBMD) by dividing the medial tibial periarticular BMD by the lateral measure. The scan-rescan ICC was 0.997 (95% CI 0.992–0.999) within a subset of 10 people (31).

Clinical variables collected

Date of birth and date of the 48-month visit were used to calculate ages of the participants. Body mass index (BMI) was calculated using weight from the 48-month visit (kg) and height from the 36-month visit (m), the closest time point to the 48-month visit that height was measured.

All publicly available data were accessed from OAI website (<http://oai.epi-ucsf.org/datarelease/>).

Statistical analyses

Because trabecular morphometry MRIs were only obtained on one knee, usually the right knee, only one knee per participant was included in all analyses. Further, only knees with concordant knee standard radiographs and knee DXA at 48-month visit were included. Because HKA was only funded to be obtained once during the OAI, and that measure was obtained at different time points for different participants, HKA measures from any time point were included. We performed Pearson's correlations to evaluate for associations between HKA and trabecular morphometry measures and knee paBMD. We also performed correlations of HKA against age and BMI as these are traditional risk factors for OA (32). We performed stratified analyses based on radiographic OA status (Kellgren/Lawrence grade 2). Additionally we stratified the analyses based on sex.

Although HKA, or mechanical alignment, is the gold standard for assessing static alignment, within the OAI, these measures were not taken at the 48 month visit, when all the periarticular bone measures were available. Instead FTA, or anatomic alignment, which is

closely associated with HKA, was available at the OAI 48 month visit. Therefore, we performed sensitivity analyses using the adjusted FTA measures instead of HKA.

To evaluate the contribution of variability in HKA by various combinations of the periarticular bone measures, we assessed the R^2 in linear regression models.

Results

As seen in figure 2, with an a priori plan to enroll 600 participants into the study, the Bone Ancillary Study recruited 629 participants of the 1390 in the progression cohort. Of the 629 participants, 503 participants had sufficient quality knee DXAs and trabecular MRIs that could be read at the OAI 48-month visit. Of those participants, 451 had HKA readings at any of the time points. And from those participants 436 had plain radiographs that were read for FTA at the OAI 48-month visit which was our final sample.

Demographics for the participants are outlined in Table 1 and Supplemental Table A. 436 knees (420 right and 16 left knees) from as many participants had a mean age was 65.4 (9.2) years old, BMI of 29.5 kg/m², and 46% were female. Those that were in the progression cohort (n=954) but not included in this study were similar except that they had a larger percentage who were women and 32% (306 of 954) had missing radiographs at their 48 month visit. As a reminder, negative HKA values represented varus alignment and positive values represented valgus alignment. The correlation between the OAI 48-month visit adjusted FTA measures with the OAI 12 – 36 month visit HKA measures was 0.70 (95% confidence intervals [CI]: 0.65 – 0.74). HKA was associated with sex where men had a lower mean HKA compared to women (–2.3 v. –0.2, $p < 0.0001$), consistent with more varus alignment. HKA was not associated with age or BMI.

The correlation coefficient of HKA with medial:lateral paBMD, the only periarticular bone measure that was a ratio, was larger than that of any other bone measure (table 2). Those with a more varus alignment had a higher medial:lateral paBMD, aBVF, aTb.N and aTb.Th and lower aTb.Sp. Sensitivity analysis using adjusted FTA values from the OAI 48 month follow up visit were similar except that the point estimates were a slightly greater in magnitude (Supplemental table B).

In those with and without radiographic OA, medial:lateral paBMD was associated with mechanical alignment, but the strength of the association was greater in those with radiographic OA (table 2). Similarly, all the absolute measures of bone had a significant association with mechanical alignment in those with radiographic OA, but these correlations were substantially attenuated in those without radiographic OA (table 2). As with the whole group, in those with and without radiographic OA, males tended to have a more varus alignment –2.6 v –0.7, $p < 0.0001$ and –1.7 v –0.4, $p < 0.01$, respectively.

In the sex-specific analyses, there were slightly more men than women but the correlation coefficients of periarticular bone with mechanical alignment were similar and all but the trabecular thickness in women, were statistically significant (table 3). Age, and BMI were not significantly associated with mechanical alignment for men or women. Similar to what was seen in the analysis for the whole group (table 2), when further stratifying by absence or

presence of radiographic OA (tables 3), the medial:lateral paBMD was associated with mechanical alignment in those without radiographic OA, but much more so in those with radiographic OA; while the absolute measures of periarticular bone was only associated with HKA in those with radiographic OA.

In table 4, the contribution of periarticular bone measures to the variation of HKA is presented. The medial:lateral paBMD accounted for 40% of the variation in HKA in the whole cohort. When restricting the analyses to only those knees with radiographic OA, the medial:lateral paBMD accounted for 47% of the variation in HKA. However, when limiting the analyses to those knees without radiographic OA, it only accounted for 11% of the variation in HKA. For all these analyses, the addition of all the absolute measures of periarticular bone, including medial paBMD, aBVF, aTb.N, aTb.Th and aTb.Sp only marginally increased the percentage of variation in HKA that could be explained. When looking at only the absolute value of the medial paBMD, this only accounted for 12% of the variability in HKA in the whole sample, 16% in those with radiographic OA, and 0% in those without radiographic OA. All 4 trabecular morphometry measures combined performed worse than the medial paBMD alone. When the paBMD was combined with the 4 trabecular morphometry measures, the additional variability in HKA explained was only marginally improved over that of paBMD alone.

DISCUSSION

This study confirms a relationship of knee joint alignment with structural measures of the subchondral bone. This relationship was strongest for medial:lateral paBMD and static alignment. This association was present in those with and without radiographic OA but more pronounced in those with OA. Additionally, we found that absolute measures of periarticular bone, including medial paBMD, aBVF, aTb.N, aTb.Th and aTb.Sp, were associated with static alignment but this was generally only present in those with radiographic OA. Finally, little additional variation in HKA is explained by the addition of absolute measures of periarticular bone after the ratio of medial:lateral paBMD is included as an independent variable. These observations persist in analyses restricted by sex.

The relationship between static alignment and medial:lateral paBMD has previously been reported in two smaller studies ($n < 100$) preselected to have medial tibiofemoral knee OA, reporting correlations of 0.44 and 0.53 (16, 18), similar to what we observed in our study 0.63. Important differences between prior studies and the current one include that our study sample was larger, evaluating more than 400 participants, the locations of the regions of interest we used on the DXA scanner were more proximal, we included knees both with and without OA, and we did not preselect for those with medial tibiofemoral OA. Additionally, neither of the prior studies had measures of trabecular morphometry or performed additional analyses focusing on the subgroups of those without OA, men only, or women only.

The observations from our study provide potentially important insights into the natural history of knee OA. We had anticipated that periarticular bone measures would associate with static alignment in those with and without knee OA. The one bone measure that performed in this manner was the medial:lateral paBMD ratio, a relative measure of peri-

articular bone that compares the medial to the lateral compartment. This finding supports the idea that static alignment is associated with relative loading in the medial and lateral compartments, even in a pre-OA setting. Because of the cross-sectional design of our study, we cannot assign directionality of causation. It is possible that changes in peri-articular bone could predispose to the development of static alignment. Perhaps trauma to the bone, which causes an increase in bone mineral density, might lead to changes in static alignment. However, it is our conjecture that it is more likely that static alignment dictates peri-articular bone measures, where changes in static alignment then cause damage to peri-articular bone.

A finding that was somewhat surprising was that the absolute measures of periarticular bone were associated with static alignment primarily in those knees with OA, not in those without OA. This may indicate that the absolute measures of periarticular bone are identifying a construct that is present in the periarticular bone, only with the development of OA or after OA develops. For example, in a prior study, we found that in regions where bone marrow lesions are visualized on T2 weighted fat suppressed images, there is a higher aBVF, aTb.N, and aTb.Th, and lower aTb.Sp, (33) similar to the pattern seen with increased varus alignment. Thus, perhaps there are bone marrow lesions in the regions of bone indicated by higher absolute measures of periarticular bone. An alternate explanation could be that the changes observed in the periarticular bone are a consequence of bone attempting to remodel and repair after incurring damage.

A prior study has shown that medial:lateral paBMD is associated with subchondral sclerosis (10), usually a feature of more severe OA, occurring in the region where tibial paBMD is assessed. We found that in knees without OA, only 11% of the variability of static alignment is explained by the medial:lateral paBMD ratio while in knees with OA, a much higher 47% of the variability of static alignment is explained by the medial:lateral paBMD ratio. The association between static alignment and medial:lateral paBMD is stronger in those with OA perhaps because in the situation where OA exists, the relative measure of medial:lateral paBMD is increased for two reasons, the *physiologic relative changes* in periarticular bone that occur because of loading differences in the medial and lateral tibiofemoral compartments because of static alignment as well as the *pathologic changes* that occur after or when OA occurs as identified by those with a higher aBVF, aTb.N, and aTb.Th, and lower aTb.Sp. In further support of this possibility, we expected and found that the range of peri-articular bone and static alignment to be broader in those with OA compared to those without (Supplement A).

The ratio of medial:lateral paBMD is a relative measure of periarticular bone which allows for an internal control within the knee. We were only able to create this ratio for paBMD as we did not have measurements of periarticular trabecular morphometry in the lateral compartment due to financial constraints. If we did have trabecular morphometry measures in the lateral compartment, we suspect they would perform similarly to paBMD as a higher absolute paBMD is associated with greater tibial aBVF, aTb.N, tibial aTb.Th, and lower tibial aTb.Sp (34). In future studies of trabecular morphometry, ratios of the measures that would also allow for internal controls, may also prove to be more powerful than the absolute measures as is the case with DXA assessed paBMD (table 4). Greater understanding of the

relationship between static alignment and periarticular bone changes could have important implications regarding treatment targets for knee OA.

In this study, DXA assessed paBMD performs similarly to the trabecular morphometry measures, but it is much easier to acquire and measure DXA compared with MRI assessed trabecular morphometry. Additionally, DXA scanners are almost ubiquitous in a clinical setting as they are widely used to assess for osteoporosis. Therefore, there is an opportunity to consider its use to measure paBMD as an early biomarker for OA. However, in order to understand paBMD in OA, it is critical to understand that DXA assessed paBMD is a measure of apparent bone mineral density, not material density. Apparent density is bone mass/total volume of bone (includes volume occupied by bone marrow) whereas material density is bone mass/bone volume (excludes volume occupied by bone marrow) (35). Based on histology, OA bone has a lower material bone density but a higher apparent density compared to non-OA peri-articular bone (36). Although it might seem intuitive to expect that material density might be more informative than apparent density as it provides a more precise measure of bone mineralization, in OA, apparent density associates with bone stiffness whereas material density does not (36). Stiffness is a measure of resistance offered by a body to deform, or a measure of the amount of force required to cause a displacement in the direction of the force applied. Bone that is stiffer is less able to absorb energy in the setting of mechanical impact (37). In OA, those with a higher apparent density have greater peri-articular bone stiffness, meaning bone with higher apparent BMD requires more force to compress a given amount than bone with lower apparent BMD. Perhaps the pathologic changes detectable with trabecular morphometry contribute to a higher apparent BMD and confer greater stiffness to bone.

There is some existing evidence supporting the possibility that modifying static alignment can influence periarticular bone, including a study by Akamatsu et al where a group of participants with medial knee OA (n = 20), identified for high tibial osteotomy, had their periarticular bone density assessed prior to the surgical intervention and subsequent to the procedure (38). A high tibial osteotomy is an extreme method of modifying static alignment. The medial:lateral paBMD ratios were high pre-operatively and decreased post-operatively, suggesting that an effort to alter static alignment might confer changes in periarticular bone, though we must point out that there was no comparator arm in this study. Additionally, less extreme interventions may also modify static alignment, such as knee bracing. In a study (n = 14) by Katsuragawa et al, all participants had a varus knee, upon which a valgus brace was applied; after 3 months of follow up, the braced knees had statistically significant improvement in the tibial paBMD ratio, not seen in the unbraced knees(39). However, similar to the study by Akamatsu et al, this was a small study with no comparator arm. Larger randomized controlled studies of tibial osteotomy and knee bracing are needed to confirm whether these interventions targeting static alignment can modify periarticular BMD.

There are several limitations of this study. First, MRI provides only indirect measurements of parameters of bone morphology. Only direct histology, which is difficult to acquire in those with milder or without disease, would allow direct measurements; but in the absence of such information, surrogate measures must be used to extrapolate measurements such as

trabecular thickness and spacing. An additional limitation to this study is that HKA, the gold standard assessment of static alignment, and periarticular bone measures were generally not assessed at the same visit because inclusion of HKA and trabecular morphometry measures were funded by separate ancillary projects to the OAI and were included when convenient, taking into consideration the entire study schedule. To address this limitation, we performed sensitivity analyses using adjusted FTA that were all contemporaneous with the periarticular bone measures instead of HKA and found similar results (Supplemental table B) to the main results using HKA (table 2). An additional limitation is that a longitudinal study would be needed to assess causation in the relationship between static alignment and periarticular bone abnormalities. Because HKA was only obtained at one time point in our study, we were unable to test this relationship in our study.

In summary, static knee alignment is associated with relative paBMD as measured by DXA in those with and without OA. Absolute measures of periarticular bone are associated with static alignment in those with OA only. The variation in static alignment explained by trabecular morphometry is mostly captured with the relative paBMD measure. Understanding the underlying pathophysiology driving the aberrations in trabecular morphometry could provide important insights in identifying new targets for OA therapies, some of which may be biomechanically based. Longitudinal studies are needed to elucidate whether biomechanical alterations may alter periarticular bone in knee OA and ultimately prevent, slow, and maybe even reverse the progression of OA. Additionally, our findings indicate the potential utility of DXA and MRI-based measures to evaluate the effects of biomechanical or bone-targeted interventions for knee OA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr. Lo is supported by K23 AR062127, an NIH/NIAMS mentored award, providing funding for design and conduct of the study, analysis, and interpretation of the data; and preparation and review of this work. This work is supported in part with resources at the VA HSR&D Center for Innovations in Quality, Effectiveness and Safety (#CIN 13-413), at the Michael E. DeBakey VA Medical Center, Houston, TX. Periarticular Bone Density as a Biomarker for Early Knee Osteoarthritis was sponsored by NIH/NIAMS (McAlindon R01 AR 060718) providing support for design and conduct of the study, analysis, and interpretation of the data; and preparation and review of this work. The Osteoarthritis Initiative is a public-private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institutes of Health, a branch of the Department of Health and Human Services, and conducted by the Osteoarthritis Initiative Study Investigators. Private funding partners include Merck Research Laboratories; Novartis Pharmaceuticals Corporation, GlaxoSmithKline; and Pfizer, Inc. Private sector funding for the Osteoarthritis Initiative is managed by the Foundation for the National Institutes of Health.

References

1. Cisternas MG, Murphy L, Sacks JJ, Solomon DH, Pasta DJ, Helmick CG. Alternative Methods for Defining Osteoarthritis and the Impact on Estimating Prevalence in a US Population-Based Survey. *Arthritis Care Res (Hoboken)*. 2016; 68:574–580. [PubMed: 26315529]
2. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II Arthritis Rheum. 2008; 58:26–35. [PubMed: 18163497]

3. Findlay DM, Atkins GJ. Osteoblast-chondrocyte interactions in osteoarthritis. *Curr Osteoporos Rep.* 2014; 12:127–134. [PubMed: 24458429]
4. Yuan XL, Meng HY, Wang YC, Peng J, Guo QY, Wang AY, et al. Bone-cartilage interface crosstalk in osteoarthritis: potential pathways and future therapeutic strategies. *Osteoarthritis Cartilage.* 2014; 22:1077–1089. [PubMed: 24928319]
5. Radin EL, Paul IL, Lowy M. A comparison of the dynamic force transmitting properties of subchondral bone and articular cartilage. *J Bone Joint Surg Am.* 1970; 52:444–456. [PubMed: 5425639]
6. Sharma L, Song J, Dunlop D, Felson D, Lewis CE, Segal N, et al. Varus and valgus alignment and incident and progressive knee osteoarthritis. *Ann Rheum Dis.* 2010; 69:1940–1945. [PubMed: 20511608]
7. Sharma L, Chmiel JS, Almagor O, Felson D, Guermazi A, Roemer F, et al. The role of varus and valgus alignment in the initial development of knee cartilage damage by MRI: the MOST study. *Ann Rheum Dis.* 2013; 72:235–240. [PubMed: 22550314]
8. Lo, GH., Zhang, Y., McLennan, C., Niu, J., Kiel, DP., McLean, RR., et al. Osteoarthritis Cartilage. Vol. 14. England: 2006. The ratio of medial to lateral tibial plateau bone mineral density and compartment-specific tibiofemoral osteoarthritis; p. 984-990.
9. 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; 139:330–336. [PubMed: 12965941]
10. Lo GH, Zhang Y, McLennan C, Niu J, Kiel DP, McLean RR, et al. The ratio of medial to lateral tibial plateau bone mineral density and compartment-specific tibiofemoral osteoarthritis. *Osteoarthritis Cartilage.* 2006; 14:984–990. [PubMed: 16765066]
11. 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; 52:2814–2821. [PubMed: 16145676]
12. Lo GH, Schneider E, Price L, Driban J, Tassinari A, Nevitt M, et al. Periarticular bone density and trabecular morphology predict knee oa structural progression. *Osteoarthritis and Cartilage.* 20:S76–S77.
13. Lo GH, Tassinari AM, Driban JB, Price LL, Schneider E, Majumdar S, et al. Cross-sectional DXA and MR measures of tibial periarticular bone associate with radiographic knee osteoarthritis severity. *Osteoarthritis Cartilage.* 2012; 20:686–693. [PubMed: 22430052]
14. Akamatsu Y, Koshino T, Saito T, Wada J. Changes in osteosclerosis of the osteoarthritic knee after high tibial osteotomy. *Clin Orthop.* 1997:207–214.
15. Dore D, Quinn S, Ding C, Winzenberg T, Jones G. Correlates of subchondral BMD: a cross-sectional study. *J Bone Miner Res.* 2009; 24:2007–2015. [PubMed: 19453266]
16. Thorp LE, Wimmer MA, Block JA, Moision KC, Shott S, Goker B, et al. Bone mineral density in the proximal tibia varies as a function of static alignment and knee adduction angular momentum in individuals with medial knee osteoarthritis. *Bone.* 2006; 39:1116–1122. [PubMed: 16782419]
17. Sepriano A, Roman-Blas JA, Little RD, Pimentel-Santos F, Arribas JM, Largo R, et al. DXA in the assessment of subchondral bone mineral density in knee osteoarthritis--A semi-standardized protocol after systematic review. *Semin Arthritis Rheum.* 2015; 45:275–283. [PubMed: 26188773]
18. Wada M, Maezawa Y, Baba H, Shimada S, Sasaki S, Nose Y. Relationships among bone mineral densities, static alignment and dynamic load in patients with medial compartment knee osteoarthritis. *Rheumatology (Oxford).* 2001; 40:499–505. [PubMed: 11371657]
19. Beuf O, Ghosh S, Newitt DC, Link TM, Steinbach L, Ries M, et al. Magnetic resonance imaging of normal and osteoarthritic trabecular bone structure in the human knee. *Arthritis Rheum.* 2002; 46:385–393. [PubMed: 11840441]
20. Majumdar S, Kothari M, Augat P, Newitt DC, Link TM, Lin JC, et al. High-resolution magnetic resonance imaging: three-dimensional trabecular bone architecture and biomechanical properties. *Bone.* 1998; 22:445–454. [PubMed: 9600777]
21. Driban JB, Barbe MF, Amin M, Kalariya NS, Zhang M, Lo GH, et al. Validation of quantitative magnetic resonance imaging-based apparent bone volume fraction in peri-articular tibial bone of cadaveric knees. *BMC Musculoskelet Disord.* 2014; 15:143. [PubMed: 24779374]

22. Nevitt, M., Felson, D., Lester, G. The Osteoarthritis initiative: protocol for the Cohort Study.
23. Central Assessment of Full-Limb X-rays for Frontal Plane Lower Limb Alignment. [https://oai.epi-ucsf.org/datarelease/SASDocs/flXR_KneeAlign_Descrpt.pdf]
24. Central Assessment of Longitudinal Knee X-rays for Femoral-Tibial Angle (Anatomic Alignment). [https://oai.epi-ucsf.org/datarelease/SASDocs/kXR_FTA_Duryea_descrpt.pdf]
25. Iranpour-Boroujeni T, Li J, Lynch JA, Nevitt M, Duryea J, Investigators OAI. A new method to measure anatomic knee alignment for large studies of OA: data from the osteoarthritis initiative. *Osteoarthritis Cartilage*. 2014; 22:1668–1674. [PubMed: 25278076]
26. Kraus VB, Vail TP, Worrell T, McDaniel G. A comparative assessment of alignment angle of the knee by radiographic and physical examination methods. *Arthritis Rheum*. 2005; 52:1730–1735. [PubMed: 15934069]
27. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis and Cartilage*. 15:A1–A56. [PubMed: 17320422]
28. Project 15 Test-Retest Reliability of Semi-quantitative Readings from Knee Radiographs. [https://oai.epi-ucsf.org/datarelease/SASDocs/kXR_SQ_Rel_BU_descrpt.pdf]
29. Schneider E, Lo GH, Sloane G, Fanella L, Hunter DJ, Eaton CB, et al. Magnetic resonance imaging evaluation of weight-bearing subchondral trabecular bone in the knee. *Skeletal Radiol*. 2011; 40:95–103. [PubMed: 20449585]
30. Majumdar, S., Kothari, M., Augat, P., Newitt, DC., Link, TM., Lin, JC., et al. Bone. Vol. 22. United States: 1998. High-resolution magnetic resonance imaging: three-dimensional trabecular bone architecture and biomechanical properties; p. 445-454.
31. Lo, GH., Tassinari, AM., Driban, JB., Price, LL., Schneider, E., Majumdar, S., et al. Osteoarthritis Cartilage. Vol. 20. England: Published by Elsevier Ltd; 2012. Cross-sectional DXA and MR measures of tibial periarticular bone associate with radiographic knee osteoarthritis severity; p. 686-693.
32. Felson DT. The epidemiology of knee osteoarthritis: results from the Framingham Osteoarthritis Study. *Semin Arthritis Rheum*. 1990; 20:42–50. [PubMed: 2287948]
33. Driban JB, Tassinari A, Lo GH, Price LL, Schneider E, Lynch JA, et al. Bone marrow lesions are associated with altered trabecular morphometry. *Osteoarthritis Cartilage*. 2012; 20:1519–1526. [PubMed: 22940708]
34. Lo GH, Carr K, Price LL, Schneider ES, Majumdar S, McAlindon TE. Higher Subchondral Bone Volume is Associated with Higher DXA Bone Mineral Density and Knee OA Severity. *Arthritis & Rheumatism*. 2009; 60 Abstract #1945.
35. Burr DB. The importance of subchondral bone in the progression of osteoarthritis. *J Rheumatol Suppl*. 2004; 70:77–80. [PubMed: 15132360]
36. Li B, Aspden RM. Composition and mechanical properties of cancellous bone from the femoral head of patients with osteoporosis or osteoarthritis. *J Bone Miner Res*. 1997; 12:641–651. [PubMed: 9101376]
37. Malekipour F, Whitton C, Oetomo D, Lee PV. Shock absorbing ability of articular cartilage and subchondral bone under impact compression. *J Mech Behav Biomed Mater*. 2013; 26:127–135. [PubMed: 23746699]
38. Akamatsu Y, Koshino T, Saito T, Wada J. Changes in osteosclerosis of the osteoarthritic knee after high tibial osteotomy. *Clin Orthop Relat Res*. 1997:207–214.
39. Katsuragawa Y, Fukui N, Nakamura K. Change of bone mineral density with valgus knee bracing. *Int Orthop*. 1999; 23:164–167. [PubMed: 10486029]

Figure 1.

Figure 1A: Sample coronal slice acquired using a trabecular bone sequence. The yellow arrow is indicating a sample ROI. Figure 1B. Sample knee DXA Scan with medial and lateral regions of interest marked in red.

Figure 2.
Flow diagram illustrating which participants were included into the study.

Table 1

Characteristics of included and excluded participants/knees at the 48-month visit.

	Included participants n = 436 (420 right and 16 left knees)	Excluded participants n = 954 (right knees)
Sex (Female)	46%	57%
Age (years) (Mean (SD))	65.4 (9.2)	65.7 (8.8) (n=818)
Body Mass Index (kg/m²) (Mean (SD))	29.6 (4.6)	30.0 (5.0) (n=725)
Race		
White	78%	73%
Black	20%	24%
Other	2%	3%
KL Score		
0 (% of the ones performed)	14%	12%
1 (% of the ones performed)	15%	12%
2 (% of the ones performed)	33%	33%
3 (% of the ones performed)	27%	29%
4 (% of the ones performed)	11%	14%
HKA (negative = varus) (Mean (SD))	-1.32 (3.65)	-----
Medial:Lateral paBMD (Mean (SD))	1.12 (0.15)	-----
Medial paBMD (g/cm²) (Mean (SD))	1.13 (0.22)	-----
Medial tibial aBVF (Mean (SD))	0.11 (0.07)	-----
Medial tibial aTb.N (1/mm) (Mean (SD))	0.78 (0.38)	-----
Medial tibial aTb.Th (mm) (Mean (SD))	0.13 (0.02)	-----
Medial tibial aTb.Sp (mm) (Mean (SD))	1.75 (1.33)	-----

Pearson’s Correlation coefficients of periarticular bone measures as they relate to mechanical alignment (HKA); negative angles represent varus alignment.

Table 2

Measurements	Overall				No Radiographic OA				Radiographic OA			
	n = 436				n = 123				n = 313			
	r	95% CI	Upper limit	Lower limit	r	95% CI	Upper limit	Lower limit	r	95% CI	Upper limit	Lower limit
<i>Medial:Lateral paBMD</i>	-0.63	-0.69	-0.57	-0.33	-0.48	-0.26	-0.16	-0.68	-0.74	-0.62	-0.30	-0.49
<i>Medial paBMD</i>	-0.34	-0.42	-0.26	-0.09	-0.26	-0.09	0.09	-0.40	-0.49	-0.30	-0.21	-0.41
<i>Medial tibial aBVF</i>	-0.29	-0.37	-0.20	-0.15	-0.31	-0.34	0	-0.35	-0.44	-0.25	-0.15	-0.35
<i>Medial tibial aTb.N</i>	-0.32	-0.40	-0.23	-0.08	-0.25	-0.13	0.10	-0.25	-0.35	-0.15	0.42	0.22
<i>Medial tibial aTb.Th</i>	-0.22	-0.31	-0.13	-0.08	-0.25	-0.13	0.10	-0.25	-0.35	-0.15	0.42	0.22
<i>Medial tibial aTb.Sp</i>	0.30	0.21	0.38	0.19	0.02	0.37	0.32	0.22	0.22	0.42	0.11	0.11
<i>Age</i>	0.01	-0.08	0.10	0.06	-0.12	0.24	0	-0.11	0.11	0.11	0.05	0.05
<i>BMI</i>	-0.05	-0.14	0.05	0.02	-0.16	0.20	-0.06	-0.17	0.05	0.05	0.05	0.05

Table 4

Contribution of Periparticular Bone Measures to HKA using R²

R ² for HKA					
Independent Variables	Medial:lateral paBMD	Medial:lateral paBMD, aBVE, aTb.N, aTb.Th and aTb.Sp	Medial paBMD	aBVE, aTb.N, aTb.Th and aTb.Sp	Medial paBMD, aBVE, aTb.N, aTb.Th and aTb.Sp
Whole cohort	0.40	0.41	0.12	0.11	0.14
Those with ROA	0.47	0.49	0.16	0.13	0.19
Those without ROA	0.11	0.13	0 [#]	0.05 [#]	0.05 [#]

[#] not statistically significant