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Cross-sectional DXA and MR measures of tibial periarticular bone associate with radiographic knee osteoarthritis severity[1]

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SUMMARY

Objective: We evaluated the relationship of medial proximal tibial periarticular areal bone mineral density (paBMD) and trabecular morphometry and determined whether these bone measures differed across radiographic medial joint space narrowing (JSN) scores.

Methods: 482 participants of the Osteoarthritis Initiative (OAI) Bone Ancillary Study had knee dual X-ray absorptiometry (DXA) and trabecular bone 3T magnetic resonance imaging (MRI) exams assessed at the same visit. Medial proximal tibial paBMD was measured on DXA and apparent trabecular bone volume fraction (aBV/TV), thickness (aTb.Th), number (aTb.N), and spacing (aTb.Sp) were determined from MR images. Radiographs were assessed for medial JSN scores (0–3). We evaluated associations between medial paBMD and trabecular morphometry. Whisker plots with notches of these measures versus medial JSN scores were generated and presented.

Results: Mean age was 63.9 (9.2) years, BMI 29.6 (4.8) kg/m^2, and 53% were male. The Spearman correlation coefficients between DXA-measured medial paBMD and aBV/TV was 0.61 [95% confidence interval (CI) 0.55–0.66]; between paBMD and aTb.Th was 0.38 (95%CI 0.30–0.46); paBMD and aTb.N was 0.65 (95%CI 0.60–0.70); paBMD and aTb.Sp was −0.65 (95%CI −0.70 to −0.59). paBMD and the trabecular metrics were associated with medial JSN scores.

Conclusion: The moderate associations between periarticular trabecular bone density and morphometry and their relationship with greater severity of knee OA support hypotheses of remodeling and/or microscopic compression fractures in the natural history of OA. Longitudinal studies are needed to assess whether knee DXA will be a predictor of OA progression. Further characterization of the periarticular bone in OA utilizing complementary imaging modalities will help clarify OA pathophysiology.

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Introduction

There is strong evidence that periarticular bone abnormalities (e.g., sclerosis, bone marrow lesions, and attrition) are pathologic in osteoarthritis (OA)[1–6]. Evaluation of the periarticular bone using diverse imaging modalities has the potential to increase our understanding of OA pathology occurring in this structure.

A number of OA features, including sclerosis and bone marrow lesions, have been associated with local changes in bone mineral density (BMD)[7–11]. One method of assessing local BMD changes in a given region of interest (ROI) is with dual X-ray absorptiometry (DXA) which provides a measure of apparent tibial periarticular areal BMD (paBMD) defined as [(mineralization within a ROI) divided by (area of the ROI)].

High-resolution magnetic resonance imaging (MRI) allowing for *in vivo* evaluation of trabecular bone can be obtained with parameters that optimize visualization of these structures[12–16]. In Fig. 1, we show an example MR image from a knee with moderate

[1] The views expressed in this article are those of the author(s) and do not necessarily represent the views of the Department of Veterans Affairs.

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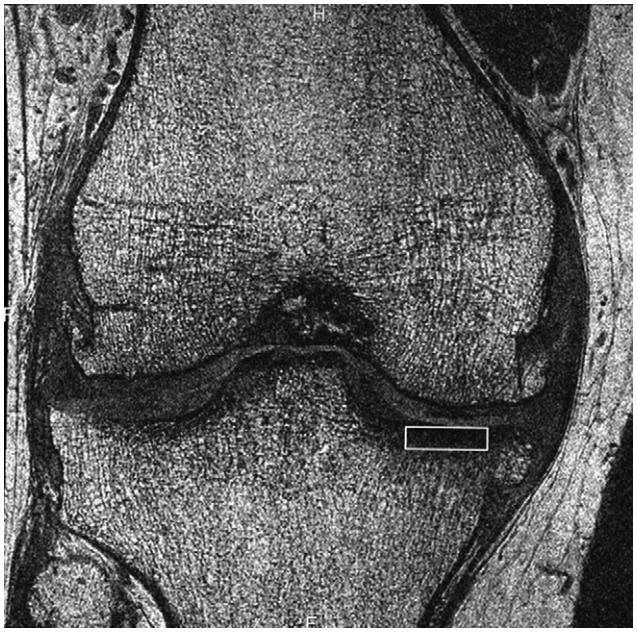

Fig. 1. Trabecular magnetic resonance image of a knee with medial tibiofemoral OA JSN grade 3. Marrow fat appears white (high-intensity signal) while bone appears black (no signal). The white rectangle is a sample ROI.

OA. On these images, the marrow fat has a high-intensity signal (e.g., appears white) while bone has no signal (e.g., appears black). Using this image contrast, there is an opportunity to calculate apparent trabecular bone volume fraction (aBV/TV), defined as trabecular bone volume divided by total ROI volume, as well as apparent morphometric assessments of trabecular number (aTb.N), thickness (aTb.Th) and spacing (aTb.Sp.).

Knee DXA has the potential to predict OA progression and therefore indicates the need for early and/or preventative treatment. This study serves to provide initial validation needed to support the use of knee DXA in this manner. By obtaining knee DXAs, trabecular MRIs, and knee X-rays on the same joint and at the same time point, we have the opportunity to better understand structural patterns that underlie the previously reported greater paBMD in those with greater knee OA severity[7,8]. Therefore, the goals of this study were (1) to evaluate the relationship of medial tibial paBMD as measured by DXA with medial tibial aBV/TV, aTb.N, aTb.Sp, and aTb.Th as measured by MRI and (2) to evaluate each measure subgrouped across medial tibial-femoral joint space narrowing (JSN) scores, a radiographic measure of OA severity.

Methods

Study design

This is a cross-sectional study of a convenience sample of participants of the Bone Ancillary Study, an ancillary study to the Osteoarthritis Initiative (OAI), including only those with complete OAI 30 or 36 months knee DXAs and trabecular MR morphometry metrics and OAI 36 months radiographic medial JSN readings.

Sample selection

The OAI is a publicly available multi-center observational study of knee OA of 4796 participants, which is comprised three groups classified at baseline, the progression ($N = 1389$), the incidence ($N = 3285$), and a nonexposed control group ($N = 122$). The "progression subcohort" all have pre-existent symptomatic radiographic knee OA (ROA), the "incident subcohort" are at increased risk for developing symptomatic ROA, and the "nonexposed control subcohort" do not have knee pain or ROA in either knee and do not have risk factors for knee OA[17].

The Bone Ancillary Study is nested within the OAI and involves members of the progression subcohort. These subjects met the subcohort's inclusion criteria of age 45–79 years; and had at least one knee with both radiographic evidence of knee OA [Osteoarthritis Research Society International (OARSI) atlas[18] osteophyte grade 1–3] and symptoms ("pain, aching or stiffness on most days of the month in the last year") at their OAI study baseline visit. Those with evidence of severe JSN, as defined by OARSI atlas[18] JSN grade 3, in both knees were excluded.

Participants were enrolled into the Bone Ancillary Study ($N = 629$) during their 30 months or 36 months OAI follow-up visit. The purpose of the Bone Ancillary Study was to evaluate the influence of bone measures on longitudinal structural progression. The final results of the Bone Ancillary Study are not yet available. Inclusion criteria for the Bone Ancillary Study were that participants were agreeable to having the additional assessments of knee trabecular MRI and DXA. Exclusion criteria into the Bone Ancillary Study were contraindication for MRI and the presence of bilateral knee replacements. At the time of enrollment into the Bone Ancillary Study, participants had a knee DXA scan and a knee trabecular MRI of the same knee. The participants of the study presented in this manuscript include those of the Bone Ancillary Study with complete baseline (OAI 30 or 36 months) knee DXA and trabecular morphometry metrics, and medial JSN data from OAI 36 months plain radiographs.

MRI

Participants had unilateral knee trabecular MRI exams on one of the four identical Siemens Trio 3T MRI systems at the clinical sites, Memorial Hospital of Rhode Island (Pawtucket, RI) Ohio State University (Columbus, Ohio), University of Pittsburgh (Pittsburgh, PA), and University of Maryland/Johns Hopkins University (Baltimore, MD). The right knee was usually scanned unless this knee was replaced or there was a contraindication for an MRI of this knee, in which case, the left knee was scanned.

Coronal-oblique 3D fast imaging with steady state precision (FISP) was used to visualize the periarticular trabecular bone. Images were obtained in 10.5 min using 72 slices, 1 mm slice thickness, 0.23 mm × 0.23 mm in-plane spatial resolution, 12 cm field of view, 512 × 512 matrix (interpolated to 1024 × 1024), 4.92 ms echo time (fat-water in-phase), 20 ms recovery time, 50° flip angle, 180 Hz/pixel readout bandwidth, and phase encode right/left. Interpolation does not change the measured spatial resolution, but does change the displayed spatial resolution. It does not affect metrics taken from the images. The chemical shift artifact (signal void in the distal femur) was 2.4 pixels, intentionally shifted superiorly so that it was outside the femoral subchondral bone and the tibial ROI.

Trabecular MR image analysis

One analyst (AT) determined all the tibial trabecular morphometry metric values (aBV/TV, aTb.N, aTb.Th, and aTb.Sp) using an established proprietary software, calcDCN used in prior research studies to evaluate bone in osteoporosis and OA[13–15,19–22]. AT placed a rectangular ROI in the proximal medial tibia immediately adjacent to the articular cartilage. We focused on the medial compartment as medial tibiofemoral OA is more common that lateral OA. The ROI had a height of 3.75 mm and a width that varied from 14–17 mm depending on the size of the knee, and was placed

on each of 20 consecutive MRI slices central to the joint (Fig. 1). Details of the software algorithms used to derive these metrics have been reported[22]. In brief, aBV/TV is the percent of the number of pixels contributing to the bone signal void normalized to the total number of pixels in the ROI. The aTb.Th is determined using the mean value of the mean intercept length for all angles through a given image, measured in millimeters. The aTb.N is calculated by dividing the aBV/TV by aTb.Th. And finally, aTb.Sp is calculated using the equation (1/aTb.N) − aTb.Th. An average of each of the metrics was taken across the 20 ROIs within one knee. Intra-rater (measurement–remeasurement) reliability was good with intra-class correlations (ICC): 0.97 [95% confidence interval (CI) 0.91–0.99] for aBV/TV, 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. For the reliability sample, $N = 12$ inclusive of all clinical sites, with each pair of scans being assessed at least 3 days apart. The reliability sample included some volunteers who were not part of the OAI and hence were not screened for the presence or absence of symptoms or radiographic OA. The measurement range and standard deviation (SD) of the test–retest analysis differences were as follows: for aBV/TV, the smallest and largest paired differences were −0.019 and 0.061 and SD of the differences was 0.022; for aTb.Th, the smallest and largest paired differences were −0.009 and 0.010 and SD of the differences was 0.007; for aTb.N, the smallest and largest paired differences were −0.078 and 0.398 and SD of the differences was 0.128; and for aTb.Sp, the smallest and largest paired differences were −0.527 and 0.123 and SD of the differences was 0.169.

Tibial plateau DXA

The proximal tibiae were evaluated using one of the four identical DXA scanners (Lunar Prodigy Advance scanner, GE Lunar Corp., Madison WI, USA) at the four clinical sites with investigational knee software (enCORE 2007 Version 11.20.068) provided by the manufacturer. The lower extremity was positioned with the long axis of the tibia perpendicular to the X-Ray beam, and neutrally rotated. A foam positioner was placed posterior to the popliteal fossa to put the knee in mild flexion. The ipsilateral foot was then placed into the foot-positioner and securely wrapped with the velcro strap around the perimeter of the foot and the positioner. This positioning resulted in the ipsilateral toes perpendicular to the scanning bed with the plantar surface of the foot adjacent to the perpendicular edge of the positioner which was parallel to the lower border of the scanner bed. The positioning laser light was used to center the scanner arm 5 cm below the inferior pole of the patella. The knee was then imaged by the DXA scanner. A sample image is seen in Fig. 2.

Tibial plateau BMD measurements

The height of each proximal medial tibial ROI was fixed at 10 mm while the ROI width in the medio-lateral direction was set as ½ the distance between the medial and lateral bone edges along a line midway between the far medial and lateral points of the tibial plateau (Fig. 2). The length of bone edges served as the outer dimension of the ROIs. The ROIs were positioned so that their top edges were just superior and parallel to the medial joint surfaces of the tibia. The scan–rescan (with repositioning) ICC was 0.997 (95%CI 0.992–0.999) for the right medial tibial areal BMD evaluating a sample of 10 individuals. The reliability sample included some volunteers who were not part of the OAI and hence were not screened for the presence or absence of symptoms or radiographic OA. The smallest and largest paired remeasurement differences were −0.026 and 0.031 and SD of the paired differences was (0.017).

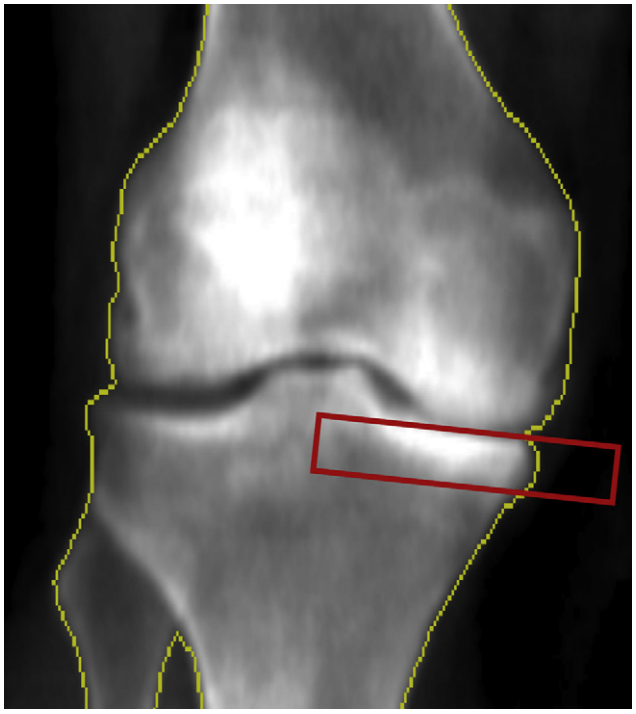

Fig. 2. DXA of the same knee scanned in Fig. 1 with medial tibiofemoral OA with JSN grade 3. The red rectangle bounded by the yellow bone border is the ROI used to measure the medial tibial paBMD.

Plain radiographs of the knee

A weight-bearing, bilateral, fixed flexion posterior–anterior (PA) radiograph of the knees was obtained at the OAI 36 months visit. These images were scored for JSN grade (0–3) using the OARSI atlas[18] [weighted kappa (intra-rater reliability) = 0.88 (95%CI 0.80–0.95)] by the Boston University X-ray reading group, results that were made publicly available on the OAI website (http://oai.epi-ucsf.org/datarelease/) with the filename, kXR_SQ_BU05_SAS, Version 5.4.

Statistical analysis

Because only unilateral trabecular MR images were acquired, we focused all our analyses on this knee. We performed Spearman's correlations and created scatter plots of medial paBMD versus all apparent trabecular morphometry metrics (average of the 20 slices evaluated on each MRI). Whisker plots with notches of paBMD and the trabecular morphometry measures versus medial JSN scores were generated and presented. The Kruskal–Wallis test was used to generate global *P*-values for these comparisons. If the global test was statistically significant, pairwise comparisons were made using the Mann–Whitney *U* test; the medial JSN = 0 group was the referent group. All analyses were performed using SAS version 9.2 with the exception of the ICC calculations which were performed using SPSS version 19. *P*-values <0.05 were considered statistically significant.

Results

482 participants were included in this study. The mean age was 63.9 (9.2) years, BMI 29.6 (4.8) kg/m^2, and 53% were male. Of the knees studied, 466 (97%) were right knees, and 16 (3%) were left.

224 knees had a medial JSN score of 0, 124 with a JSN of 1, 109 with a JSN of 2, and 29 with a JSN of 3.

Figure 3 illustrates scatter plots of paBMD versus the trabecular morphometry measures of all participants. The Spearman correlation coefficients between the medial paBMD and aBV/TV, aTb.N, aTb.Th, and aTb.Sp were 0.61, 0.65, 0.38, and −0.65 respectively, each with $P < 0.0001$.

The overall comparison evaluating paBMD and MRI trabecular measures across medial JSN scores was statistically significant (Fig. 4). Pairwise comparisons indicated that paBMD, aBV/TV, aTb.N, and aTb.Th were statistically greater among knees with higher medial JSN scores (JSN = 2 and JSN = 3) than knees with medial JSN = 0. Pairwise comparisons also showed that for paBMD, aBV/TV, and aTb.N, knees with medial JSN = 1 versus JSN = 0 had also statistically greater values. aTb.Sp was statistically significantly lower in knees with higher medial JSN (JSN = 1–3) compared with knees having a JSN = 0.

Discussion

In this study of the proximal medial tibial periarticular bone, the areal paBMD measured by DXA correlated positively with aBVF, aTb.N, and aTb.Th and negatively with aTb.Sp. Further, each of these measures was also associated with medial JSN score, a radiographic marker of OA severity.

Elevated apparent paBMD, as measured by DXA, has been associated with many features of OA including osteophytes[8], JSN[8], sclerosis[8], bone marrow lesions[7], meniscal damage[23], and longitudinal JSN[10,24]. We confirmed that elevated paBMD is associated with medial JSN as well as with periarticular apparent trabecular measures ascertained using MRI. Apparent BMD has been associated with bone stiffness[25], a characteristic of bone that has been implicated in OA pathophysiology[26]. Our findings that higher paBMD was associated with greater aBV/TV, aTb.N, and aTb.Th and lower aTb.Sp, each of which was correlated with greater medial JSN suggesting potential pathologic etiologies for these findings including bone remodeling or small compression fractures (e.g., microcracks) occurring in these regions of periarticular bone[6,27]. A histologic study of osteoarthritic hips removed at the time of joint replacement corroborates our findings showing that DXA-measured BMD and histomorphometry measured bone volume fraction are highly correlated $r = 0.77–87$, $P < 0.001$[28]. Furthermore, evidence of microdamage, including microcracks and microfractures, was frequently observed in histologic samples of osteoarthritic joints at the time of replacement[28–30].

To our knowledge, there have been two reports evaluating MRI trabecular morphometry as it relates to knee OA severity though the relationship with paBMD measured by DXA was not evaluated. Blumenkrantz *et al.* showed an opposite finding to ours where medial tibial bone in those knees with more severe radiographic OA

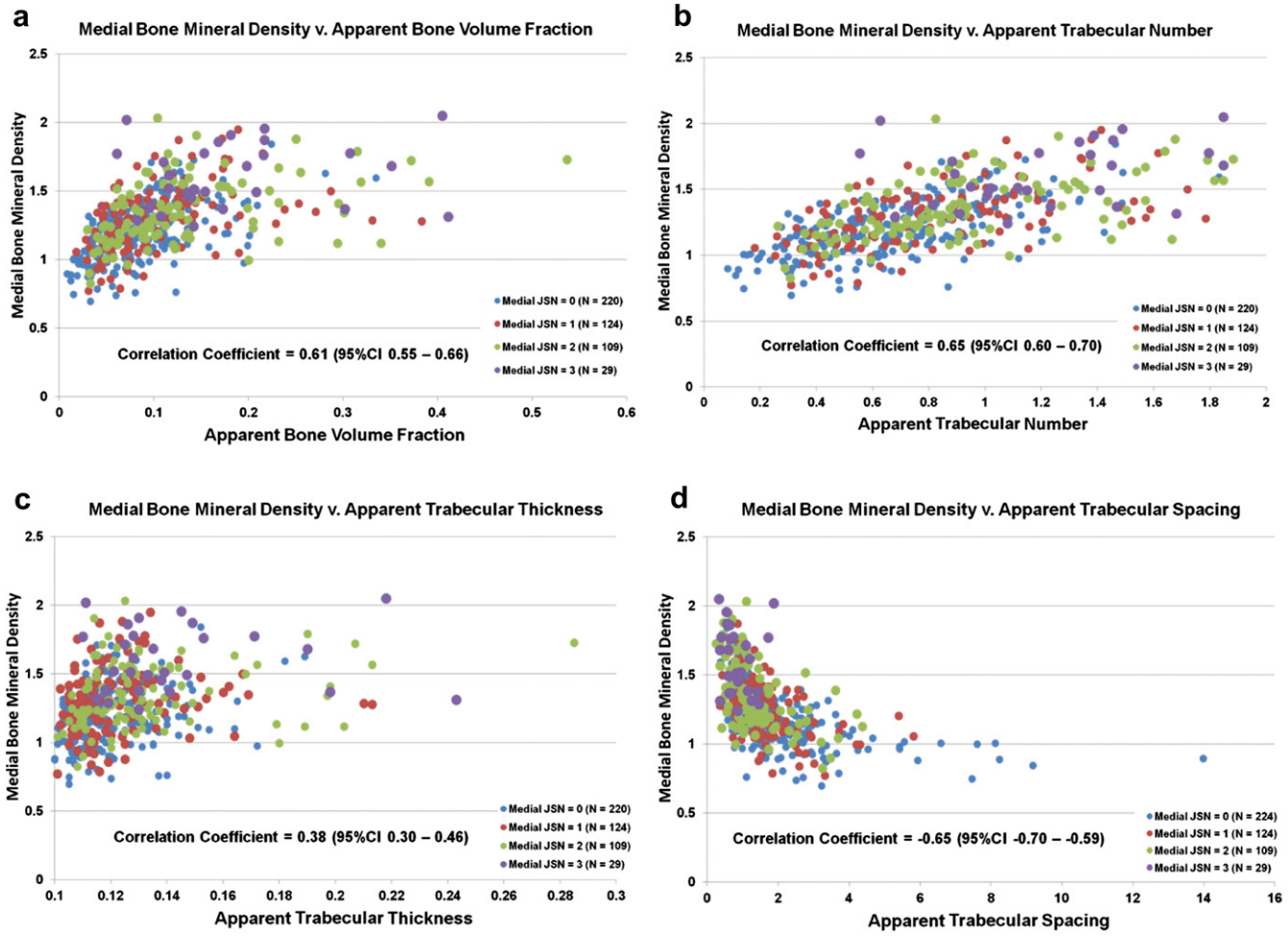

Fig. 3. Scatter plots ($N = 482$) of the proximal medial tibial paBMD (g/cm^2) determined by DXA, versus MRI measured (a) the tibial apparent bone volume fraction (aBV/TV), (b) the apparent trabecular number (aTb.N) (1/mm), (c) apparent trabecular thickness (aTb.Th) (mm), (d) the apparent trabecular spacing (aTb.Sp) (mm). The points are color coded to the knee medial JSN scores.

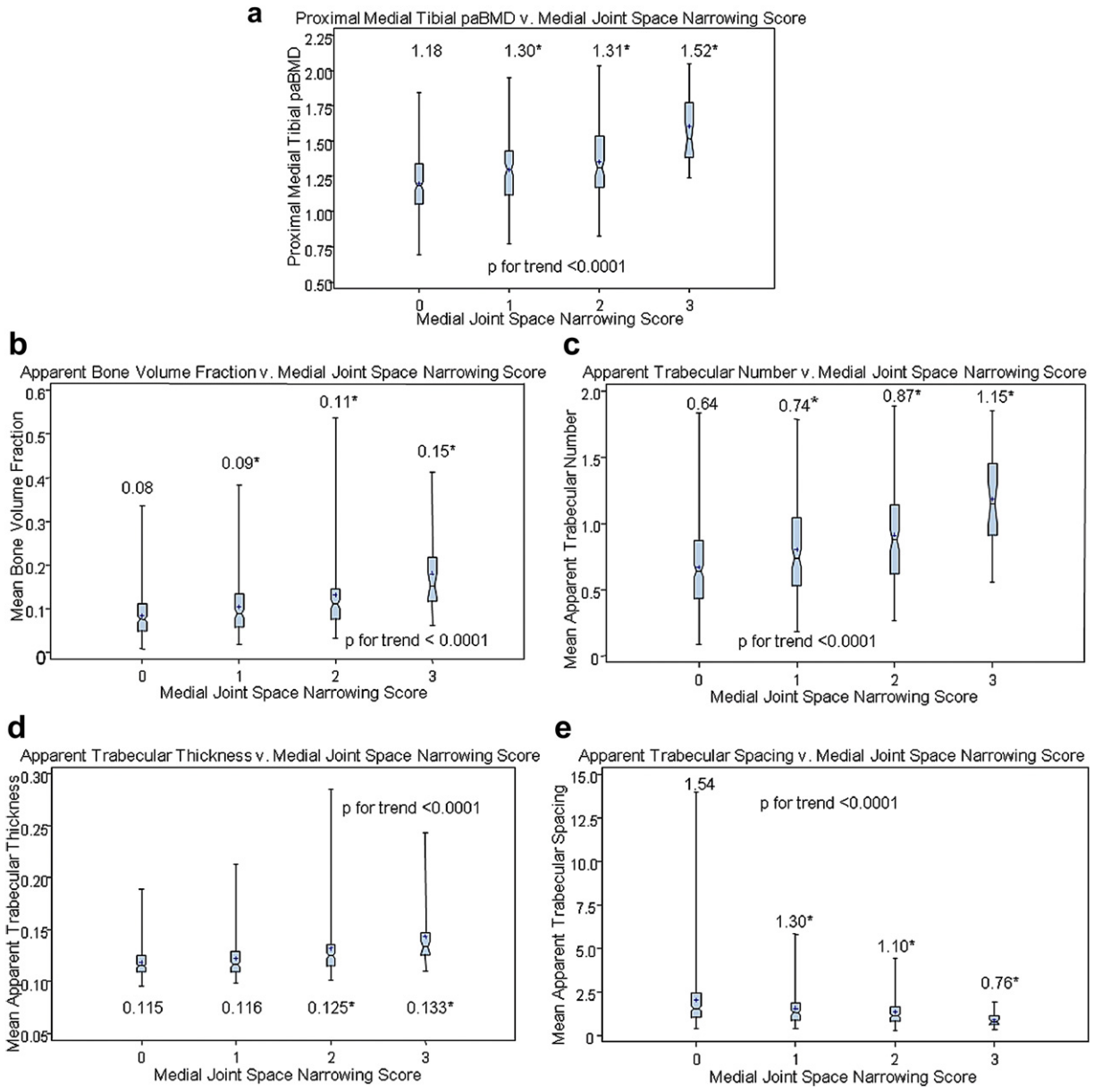

Fig. 4. Whisker plots with notches by medial JSN score of (a) proximal medial tibial paBMD, (b) apparent bone volume fraction (aBV/TV), (c) apparent trabecular number (aTb.N) (1/mm), (d) apparent trabecular thickness (aTb.Th) (mm), and (e) apparent trabecular spacing (aTb.Sp) (mm). Values above whisker plots are median values in the respective medial JSN groups. *Denotes statistically significant difference ($P < 0.05$) compared to the referent group, knees with a medial JSN score = 0.

had a lower aBV/TV and higher aTb.N compared to those with mild radiographic OA[14]. However, this study was small ($N = 30$) and utilized axial 1.5 T MR images which did not allow visualization of sub-articular tibial bone. In our study, the coronal oriented MR acquisition facilitated visualization of this portion of bone, likely most relevant in knee OA pathophysiology. Chiba *et al.* evaluated 60 participants and studied periarticular trabecular measures based on MR images and radiographic evidence of OA[31]. That study employed sagittal 3 T MR images which allowed evaluation of trabecular bone adjacent to the articular cartilage in a manner similar to ours and found similar results to ours; greater medial tibial JSN was associated with a greater aBV/TV and aTb.Th, and lower aTb.Sp. The results for aTb.N were similar but not statistically significant. In a study evaluating trabecular spacing on radiographs in people with knee OA who were candidates for joint replacements, Wong *et al.* found trabecular spacing was positively associated with joint space width such that narrower joint space was correlated with lower trabecular spacing[32] similar to what we found in this study.

An important limitation to our study is that the measures of trabecular morphometry are based on MR images and are not direct assessments of histomorphometry. In addition two of the trabecular morphometry metrics, aTb.N and aTb.Th, were derived from the other two, aBV/TV and aTb.Sp. However, many of the results from this study are consistent with prior studies that performed direct histologic evaluation in OA. Li *et al.* evaluated femoral head specimens ($N = 16$) obtained at the time of total hip replacement and compared them to post-mortem samples of asymptomatic hips ($N = 7$)[25]. They evaluated bone volume fraction as it relates to apparent BMD, the histologic equivalent to the measure of BMD DXA provides. Similar to our findings, they found that those with OA had a higher apparent BMD and a higher bone volume fraction compared to normal

controls. Ding *et al.* also found a similar relationship in those with early knee OA ($N = 10$) compared to normal knees ($N = 10$)[33]. There have been two additional studies evaluating knee trabecular histomorphometry including not only bone volume fraction, but also trabecular number, thickness, and spacing assessments. Kamibayashi *et al.* evaluated 11 medial tibiae from 10 patients collected from hemi- and total arthroplasties for knee OA, all of whom had varus alignment and compared these knees to four age-matched controls[34]. In that study, the OA samples had a much higher bone volume fraction compared to the normal knees and the trabecular thickness was higher in the OA samples compared to normal knees which are consistent with the findings in our study. However in contrast to our findings, trabecular number was lower and trabecular spacing was higher in OA knees compared to normal knees though the differences were not statistically significant. Bobinac *et al.* evaluated 10 tibial plateaus taken at total knee arthroplasties from 10 patients with knee OA (mean age 62.5 years) – all of whom had varus malalignment[35]. The bone volume fraction, trabecular thickness and trabecular number were greater while the trabecular spacing was lower in the medial tibia compared with the lateral tibia, consistent with the findings in our study.

A study evaluating MRI-measured morphometry measures against the direct histology would be helpful in clarifying the validity of MRI-based measures, particularly the aTb.N and aTb.Sp given the conflicting reports regarding these measures in the current literature for knees with OA. However, the large sample size is a strength of this compared to prior studies. Further, we found the aTb.N and aTb.Sp associated with an established measure of structural severity, medial JSN, giving us confidence that we have reported the correct direction of bone change associated with disease severity. A significant benefit to MRI-measured morphometry is that this non-invasive method lends itself to use in large clinical studies at multiple time points. This is in contrast to the limited size histologic studies that can only be evaluated at single time points given the invasive nature of those studies.

When evaluating scatter plots of the trabecular metrics versus the paBMD of the medial tibia subgrouped by medial tibiofemoral JSN, we observed points representing the highest values for aBV/TV, aTb.N, and aTb.Th all include knees with greater JSN severity. Therefore, one potential biologic explanation is that once the disease is initiated, an additional process in bone may occur that reduces the association between DXA and trabecular morphometry. For instance, perhaps prior to initiation of OA, DXA approximates morphometry with a fixed macrostructure. Once OA initiates, the periarticular bone is then subjected to some process such as remodeling or subchondral compression of bone that alters the previously fixed macrostructure. This however, is conjecture and the data from this study cannot confirm or refute this possibility.

Additional limitations to our study include that the ROI on the trabecular MR images was not replicated on the DXA images due to constraints of the DXA software and it was not possible to exclude anterior and posterior osteophytes from the DXA ROIs because of the projectional nature of the X-rays used to acquire these images. Also, the ROI height could potentially affect the qMRI metrics as they reflect an average of the bone assessed within the ROI. Therefore, if there was heterogeneity in the bone within the ROI, the qMRI metrics could change if the height of the ROI was modified. We chose a small ROI height because we wanted to capture the part of the bone that seemed most dynamic in those with knee OA. The expectation was that a smaller ROI height would minimize the heterogeneity within the ROI. Even with these limitations, the correlations between the DXA acquired paBMD and the MRI trabecular measures were moderate to strong, suggesting that the DXA and MRI regions were similar enough to depict the same biological/pathological process.

This study corroborates prior findings identifying that periarticular bone pathology is associated with greater OA severity[2–5,36,37]. Radin *et al.* found that trauma induced periarticular bone changes in rabbits can predicate damage in cartilage[38]. If periarticular bone pathologic changes can be slowed or even halted, perhaps there is an opportunity to limit articular cartilage damage. Observational data suggests that vitamin D, an important nutrient for bone health, could prove to be beneficial; those with a higher vitamin D level were less likely to have progression of knee OA[39]. We are awaiting final results from two randomized controlled clinical trials of vitamin D in the treatment of knee OA that will hopefully address its efficacy as a disease modifying OA drug. Although there has been observational data suggesting treatment with bisphosphonates might be beneficial in OA[40], the randomized controlled trial evaluating this treatment did not confirm its efficacy[41]. Perhaps this treatment was not effective because it targeted the catabolic activity in bone. Targeting the anabolic activity of bone may be a better strategy. There was a recent animal study supporting that the treatment with parathyroid hormone reduced cartilage scores on histology[42]. To date, there have not been human studies of parathyroid hormone or its analogs in the treatment of knee OA.

In summary, medial tibial paBMD and local trabecular morphometry measures are moderately associated with one another and each is associated with medial JSN, a radiographic marker of OA severity. Knees with higher JSN scores have higher medial paBMD, aBV/TV, aTb.Th, and aTb.N, and lower aTb.Sp. Knee DXA correlates with trabecular morphometry and JSN severity cross-sectionally; longitudinal studies are needed to assess whether knee DXA will be a predictor of OA progression and serve as an indicator for those who might benefit from early and/or preventative treatment. Further characterization of the periarticular bone in OA and pre-OA states, including evaluation of these measures with basic participant characteristics, utilizing complementary imaging modalities will help clarify OA pathophysiology.

Author contributions

GL participated in the conception and design of the study, analysis and interpretation of data, drafting the manuscript and final approval of the version submitted. AT was directly involved in data analysis, specifically analyzing the trabecular morphometry measures, revising the manuscript for important intellectual content and provided final approval of the manuscript. JD was involved in the interpretation of the data, critical analysis and interpretation of data, revision for important intellectual content and final approval of the manuscript. LP was involved in the analysis and interpretation of data, critically revising the manuscript for important intellectual content, and provided final approval of the manuscript submitted. ES was instrumental in tailoring the MRI sequences to visualize trabeculae, assisted with interpretation of data, critically revising the manuscript for important intellectual content and gave final approval of the manuscript. SM provided the license for the software used to measure trabecular morphometry, assisted in interpretation of data, critically revised the manuscript for important intellectual content and gave final approval of the version submitted. TM participated in the conception and design of the study, provided the datasets needed to perform the study, participated in interpretation of data, critically revised the manuscript for important intellectual content and provided final approval of the version submitted.

Conflict of interest

Drs Lo and McAlindon have submitted a patent application for the use of local BMD in the assessment of OA risk.

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