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Research Article

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Regional Trabecular Bone Alterations in Knee Osteoarthritis: QCT Evidence from the Knee and Lumbar Spine

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Abstract

Background: Whether knee osteoarthritis (KOA)-related trabecular bone alterations are confined to the affected knee or also occur in the lumbar spine remains unclear. We compared regional knee and lumbar volumetric bone mineral density (vBMD) between KOA patients and non-KOA controls, examined lower-limb alignment relationships with medial–lateral tibial vBMD distribution, and compared bone metabolism markers between groups.

Methods: This single-centre cross-sectional study included 46 participants (32 KOA, 14 controls). Quantitative computed tomography (QCT) measured trabecular vBMD at the medial and lateral tibial plateaus (TM, TL), medial and lateral femoral condyles (FM, FL), and lumbar spine (LS);

the hip–knee–ankle angle (HKA) was measured on weight-bearing full-length radiographs. vBMD–KOA associations were examined with Firth penalised-likelihood logistic regression adjusted for age, sex, and body mass index (BMI). Medial–lateral vBMD differences were assessed with paired Wilcoxon signed-rank tests, and between-group tibial vBMD distribution with a linear mixed-effects model. HKA–vBMD-difference associations used correlation and regression. Principal bone-metabolism markers (25-hydroxyvitamin D [25(OH)D], N-MID osteocalcin, β-CTX) were compared with false discovery rate (FDR) correction.

Results: After adjustment for age, sex, and BMI, each 1-SD increase in TM, TL, and LS vBMD was associated with adjusted odds ratios (ORs) for KOA of 0.34 (95% CI 0.11–0.80), 0.38 (0.13–0.98), and 0.53 (0.24–0.99), respectively; FM and FL showed no significant adjusted association. Within the KOA group, TM vBMD exceeded TL vBMD ($P = 0.015$), whereas the two were comparable in controls ($P = 0.903$); the group × compartment interaction was not significant ($P = 0.259$). HKA was smaller in KOA ($P < 0.001$); HKA–regional vBMD associations did not remain significant after correction. KOA also showed lower 25(OH)D and higher β-CTX (FDR $q = 0.006$ for both); adjusted ORs per 1-SD increase were 0.46 (0.19–0.88) and 2.97 (1.26–9.15). N-MID did not differ between groups.

Conclusions: KOA was associated with a region-specific pattern of lower trabecular vBMD, primarily involving both the medial and lateral tibial plateaus and the lumbar spine, alongside lower 25(OH)D levels. These findings suggest that KOA-related changes in bone mass are not confined to the affected knee and may reflect both localised bone remodelling and broader skeletal characteristics, providing a rationale for further longitudinal studies of regional QCT phenotypes.

Keywords: knee osteoarthritis; quantitative computed tomography; volumetric bone mineral density; subchondral bone; lumbar spine; bone metabolism

Background

Knee osteoarthritis (KOA) is a major cause of pain, impaired mobility, and structural joint damage in middle-aged and older adults, and its burden continues to grow [1, 2]. Although cartilage degeneration is a defining feature of KOA, subchondral bone remodelling [3–5] and alterations in the local cellular, vascular, and mechanical environment also contribute to disease progression and pain [6]. Whether these bone changes are confined to the affected knee or also occur at distant skeletal sites, such as the lumbar spine, remains unclear.

The relationship between KOA and osteoporosis remains unclear [7], partly because studies have assessed different bone compartments using different imaging methods. Conventional radiographs depict structural features such as osteophytes and subchondral sclerosis, whereas dual-energy X-ray absorptiometry (DXA) measures areal bone mineral density, which can be influenced by osteophytes, cortical sclerosis, and other degenerative changes [8]. Radiographic subchondral sclerosis therefore does not necessarily indicate higher bone density in the deeper trabecular compartment.

Three-dimensional quantitative imaging allows the assessment of different tissue layers and anatomical regions within subchondral bone. Studies using quantitative computed tomography (QCT), high-resolution peripheral quantitative computed tomography (HR-pQCT), and conventional CT have shown that KOA-related bone changes are spatially heterogeneous [9, 10], varying by anatomical subregion [5, 11, 12], depth beneath the articular surface, and extent of meniscal coverage [13, 14]. Changes in the subchondral bone plate, deeper trabecular bone density, and regional trabecular remodelling may coexist within the same knee. Averaging bone density across an entire tibial plateau or femoral condyle may obscure this spatial heterogeneity.

These imaging approaches have been used to quantify regional variations in periarticular bone density [11, 12, 13]. Other studies have characterised the hip–knee–ankle angle (HKA) [15] and examined lower-limb alignment, periarticular bone density, and broader skeletal status across knee and hip OA [5, 16, 17]. Alignment has also been related to trabecular microarchitecture and structural features of OA [5, 18, 19]. However, direct evidence linking lumbar QCT measures of systemic bone status to lower vBMD in the deep trabecular bone of the tibial plateau within the same individuals remains limited. Few studies have examined knee bone mass, lower-limb alignment, and bone metabolism markers together. We therefore measured volumetric bone mineral density (vBMD) in the trabecular bone of the tibial plateau, femoral condyles, and lumbar spine within the same cohort and time frame, incorporating HKA and bone metabolism markers to compare regional patterns between patients with clinically diagnosed KOA and non-KOA controls. Our aims were to characterise the distribution of KOA-related bone changes within the knee and their relationship to lumbar bone mass, determine whether lower lumbar vBMD coexisted with lower tibial plateau vBMD, and inform future studies evaluating lumbar QCT as a potential indicator of regional low bone mass in the knee.

Methods

This was a single-centre, cross-sectional observational study. Between September 2023 and October 2025, we consecutively enrolled participants who met the inclusion criteria and completed knee QCT, lumbar QCT, and standing full-length anteroposterior radiography of both lower limbs. Of the 276 individuals initially screened, 230 were excluded, leaving 46 participants for the final analysis (32 with KOA and 14 non-KOA controls).

Study population

The inclusion criteria were: (1) age 40–80 years; (2) a history of knee pain or other knee-related symptoms; (3) completion of conventional knee radiography, knee QCT, lumbar QCT, and standing full-length anteroposterior radiography of both lower limbs during the clinical visit, with images of sufficient quality for measurement; and (4) complete clinical and imaging data.

The exclusion criteria were: (1) rheumatic or autoimmune joint disease; (2) long-term use of medications affecting bone metabolism; (3) metabolic bone disease; (4) age outside the prespecified range; (5) previous knee surgery or acute knee trauma within the preceding year; (6) missing or uninterpretable knee QCT images or missing essential imaging examinations; and (7) refusal to participate or incomplete clinical data.

Group assignment was based on clinical diagnosis rather than radiographic grade. Participants in the KOA group had a clinical diagnosis of KOA, with no minimum Kellgren–Lawrence (K–L) grade requirement. Non-KOA controls reported knee symptoms during the same period but did not meet the clinical diagnostic criteria for KOA; some had mild radiographic degenerative changes. The groups overlapped at K–L grade 2 (one participant with KOA and two controls). K–L grade was used to describe radiographic severity and in the sensitivity analysis, but not to determine group assignment. For each participant, only the more symptomatic knee, as reported by the participant, was included as the index knee.

The study was approved by the Ethics Committee of the First Affiliated Hospital of Kunming Medical University (approval no. (2025) Ethics Review L No. 58) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent. The participant flow diagram is shown in Fig. 1.

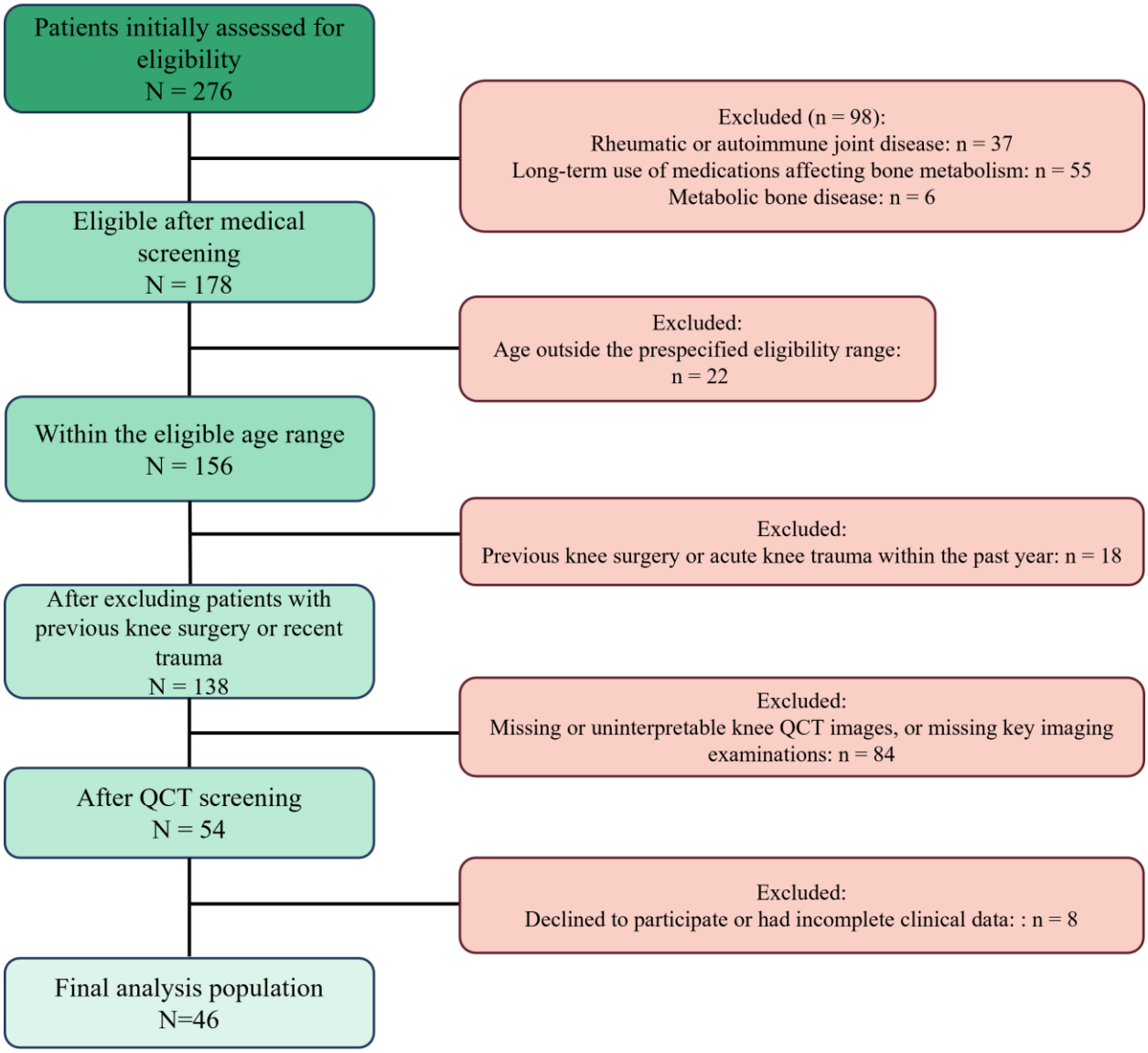


Fig. 1. Participant flow diagram

K–L grading

Two orthopaedic surgeons independently graded anteroposterior knee radiographs on a scale of 0–4 according to the Kellgren–Lawrence criteria [20]. Both readers were blinded to clinical group assignment and to each other's assessments. Inter-reader agreement was 91.3% (42/46), with a quadratically weighted κ of 0.977.

QCT measurements

All participants underwent non-contrast CT of the knee and lumbar spine. Knee CT was performed using a Philips IQon CT scanner at 120 kVp with automatic exposure control, a 512 × 512 matrix, a pitch of 1.103, a reconstructed slice thickness of 1.0 mm, and a slice interval of 0.7 mm. Phantom calibration and vBMD calculation (mg/cm³) were performed using a Mindways Model 4 calibration phantom and Mindways QCT Pro software (Mindways Software Inc., Austin, TX, USA). Knee vBMD was measured in the subchondral trabecular bone of the medial tibial plateau (TM), lateral tibial plateau (TL), medial femoral condyle (FM), and lateral femoral condyle (FL). An elliptical region of interest (ROI) was placed in the trabecular bone beneath the subchondral plate, encompassing as much of the target region as possible while excluding the subchondral plate and surrounding cortical bone. Representative ROI placement for the four knee regions is shown in Fig. 2.Each region was measured three times, and the mean value was used for statistical analysis.

Lumbar vBMD was measured in the trabecular bone of the L1–L3 vertebral bodies. If any of these vertebrae had a fracture, internal fixation, or measurement artefact, L4 was substituted. QCT Pro calculated trabecular vBMD for each vertebral body, and the mean of the vertebral measurements was used as lumbar trabecular vBMD (LS). All QCT measurements were performed by the same reader. Previous regional CT studies support interpreting these measurements in relation to anatomical location and depth [5, 11, 13].

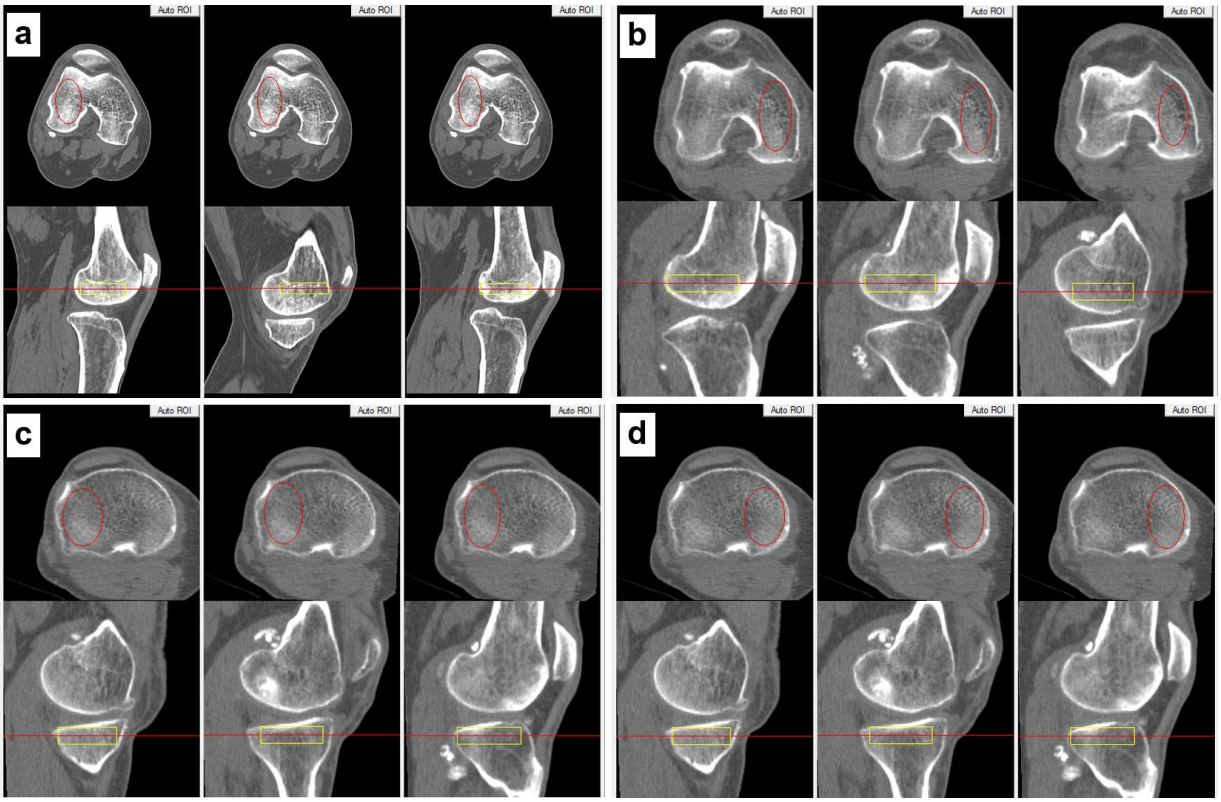


Fig. 2. QCT measurement of regional knee vBMD

Phantom calibration and vBMD measurements were performed using Mindways QCT Pro software. Panels (a–d) show representative elliptical regions of interest (ROIs) in the medial femoral condyle (FM), lateral femoral condyle (FL), medial tibial plateau (TM), and lateral tibial plateau (TL), respectively. Axial images are shown in the upper row and sagittal reconstructions in the lower row. Each ROI was placed within the subchondral trabecular bone, excluding the subchondral plate and surrounding cortical bone. Each region was measured three times, and the mean value was used for statistical analysis.

Measurement of lower-limb alignment

All participants underwent standing full-length anteroposterior radiography of both lower limbs. The same reader measured the hip–knee–ankle angle (HKA) on a picture archiving and communication system (PACS) workstation, blinded to clinical group assignment and QCT

results. HKA was defined as the medial angle between the line connecting the centres of the femoral head and knee and the line connecting the centres of the knee and ankle. HKA was analysed as a continuous variable in correlation analyses. For descriptive purposes, alignment was classified as varus (<175°), neutral (175°–182°), or valgus (>182°).

Bone metabolism markers

Bone metabolism markers were obtained from the hospital's clinical laboratory system and included 25-hydroxyvitamin D [25(OH)D], alkaline phosphatase (ALP), calcitonin, serum calcium, the N-terminal midfragment of osteocalcin (N-MID), serum inorganic phosphate, and the β-C-terminal telopeptide of type I collagen (β-CTX). All markers were measured by the Department of Laboratory Medicine at the First Affiliated Hospital of Kunming Medical University using routine clinical methods. Blood samples were collected on the day of QCT or the following day. Samples for β-CTX measurement were collected in the morning after an overnight fast, whereas samples for 25(OH)D measurement were collected on the day of the clinical visit. All measurements were part of routine clinical care, with no additional blood sampling or assays performed for this study. The prespecified primary markers were 25(OH)D, N-MID, and β-CTX, representing vitamin D status, bone formation-related activity, and bone resorption, respectively. Interpretation of β-CTX followed current consensus recommendations [21]. The remaining markers were analysed exploratorily. In both groups, calcitonin concentrations were below the laboratory reporting limit in nearly half of the participants. Calcitonin was therefore reported descriptively and excluded from between-group comparisons, correlation analyses, and regression models.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range) and were compared between groups using Welch's t-test or the Mann–Whitney U test. Categorical variables are presented as number (percentage) and were compared using Fisher's exact test. The primary analysis examined the association between vBMD at each anatomical site and KOA. TM, TL, FM, FL, and LS vBMD were standardised to the SD of the corresponding measurements in non-KOA controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using Firth penalised-likelihood logistic regression adjusted for age, sex, and body mass index (BMI) [22]. In a sensitivity analysis, non-KOA controls were restricted to K–L grades 0–1, leaving 44 participants. The analysis was repeated using mean tibial plateau vBMD [(TM + TL)/2] as the exposure, and linear regression was used to estimate the adjusted between-group difference.

Within each group, medial and lateral tibial plateau vBMD and medial and lateral femoral condylar vBMD were compared using paired Wilcoxon signed-rank tests. Between-group differences in medial–lateral vBMD distribution were assessed using a linear mixed-effects model with a participant-specific random intercept and a group × compartment interaction term, adjusting for age, sex, and BMI. A linear regression model using TM − TL as the outcome was also fitted with the same covariate adjustment. Associations between HKA and TM − TL or the TM/TL ratio were assessed using Spearman's rank correlation. Separate linear regression models adjusted for KOA status, age, sex, and BMI were used to assess associations between HKA and four femorotibial vBMD differences (FL − TL, FM − TM, FM − TL, and FL − TM). P values for these four comparisons were adjusted using the Holm method.

For bone metabolism analyses, 25(OH)D, N-MID, and β-CTX were designated as the primary markers. Between-group comparisons were performed using the Mann–Whitney U test, with the

false discovery rate (FDR) controlled by the Benjamini–Hochberg procedure. Spearman's rank correlations were calculated for 18 associations between six continuous bone metabolism markers and three QCT phenotypes, and for 15 pairwise associations among the six markers. P values were adjusted separately for the two sets of analyses using the Benjamini–Hochberg procedure. The correlation between N-MID and β-CTX was further examined in the overall sample and separately in the KOA and non-KOA groups. Associations between each primary marker and KOA were examined using Firth penalised-likelihood logistic regression adjusted for age, sex, and BMI (n = 46). Effect estimates were reported per 1-SD increase, with the SD calculated from the overall sample. All tests were two-sided, with $P < 0.05$ considered statistically significant; FDR-adjusted q values were also reported where applicable. Statistical analyses were performed using R version 4.5.2.

Results

Participant characteristics, imaging features, and vBMD

A total of 46 participants were included, comprising 32 patients with KOA and 14 non-KOA controls. Baseline characteristics are presented in Table 1. Compared with non-KOA controls, patients with KOA were older (65.34 ± 8.78 vs 58.93 ± 9.68 years, P = 0.044) and had a higher proportion of women [26/32 (81.2%) vs 6/14 (42.9%), P = 0.015], while BMI did not differ significantly between groups (25.84 ± 4.50 vs 25.02 ± 4.00 kg/m², P = 0.54). The median K–L grade was 4 in the KOA group and 1 in non-KOA controls ($P < 0.001$). vBMD was lower at all five measured sites in the KOA group (Table 1). Patients with KOA also had a smaller HKA [172.0° (166.8°, 173.0°) vs 176.0° (175.0°, 177.8°), $P < 0.001$] (Fig. 4d) and a higher prevalence of varus alignment [27/32 (84.4%) vs 2/14 (14.3%), $P < 0.001$].

Table 1. Baseline characteristics of patients with clinical KOA and non-KOA controls

Variable		Non-KOA controls (n = 14)	KOA group (n = 32)	P value
Sex, n	Female	6 (42.9%)	26 (81.2%)	0.015
	Male	8 (57.1%)	6 (18.8%)	
Age, years		58.93 ± 9.68	65.34 ± 8.78	0.044
BMI, kg/m²		25.02 ± 4.00	25.84 ± 4.50	0.541
K–L grade,n (0/1/2/3/4)		2/10/2/0/0	0/0/1/5/26	<0.001
HKA (°)		176.0 [175.0, 177.8]	172.0 [166.8, 173.0]	<0.001
Alignment category	Varus	2	27	<0.001
	Neutral	12	5	
	Valgus	0	0	
QCT vBMD, mg/cm³	TM	122.85 ± 32.39	96.89 ± 28.78	0.017
	TL	123.10 ± 47.40	81.86 ± 30.80	0.008
	FM	127.80 ± 29.76	103.87 ± 35.55	0.025
	FL	168.02 ± 48.16	125.50 ± 41.71	0.009
	LS	91.77 ± 19.35	72.39 ± 20.44	0.005

Data are presented as mean ± standard deviation, median (interquartile range), or number (percentage). Between-group comparisons were performed using Welch's t-test for age, BMI, and vBMD; the Mann–Whitney U test for K–L grade and HKA; and Fisher's exact test for sex and alignment category. BMI, body mass index; HKA, hip–knee–ankle angle; K–L, Kellgren–Lawrence; QCT, quantitative computed tomography; vBMD, volumetric bone mineral density.

Lower TM, TL, and LS vBMD were associated with KOA

Although vBMD was lower at all five anatomical sites in the KOA group in unadjusted comparisons (Table 1), the associations with KOA remained statistically significant only for TM, TL, and LS after adjustment for age, sex, and BMI (Fig. 3).

Firth penalised-likelihood logistic regression showed that the adjusted odds ratios (ORs) for KOA per 1-SD increase in vBMD, using the corresponding SD in non-KOA controls, were 0.34 for TM (95% CI, 0.11–0.80; P = 0.012), 0.38 for TL (95% CI, 0.13–0.98; P = 0.045), and 0.53 for LS (95% CI, 0.24–0.99; P = 0.045). The adjusted associations were not statistically significant for FM (OR = 0.68; 95% CI, 0.33–1.30; P = 0.25) or FL (OR = 0.53; 95% CI, 0.19–1.25; P = 0.15).

In a sensitivity analysis restricted to non-KOA controls with K–L grades 0–1 (n = 44), higher mean tibial plateau vBMD [(TM + TL)/2] remained associated with lower odds of KOA (OR = 0.26;

95% CI, 0.06–0.74; P = 0.009). In a separate adjusted linear regression model, mean tibial plateau vBMD was 25.5 mg/cm³ lower in the KOA group than in non-KOA controls (95% CI for the reduction, 6.9–44.0 mg/cm³; P = 0.008).

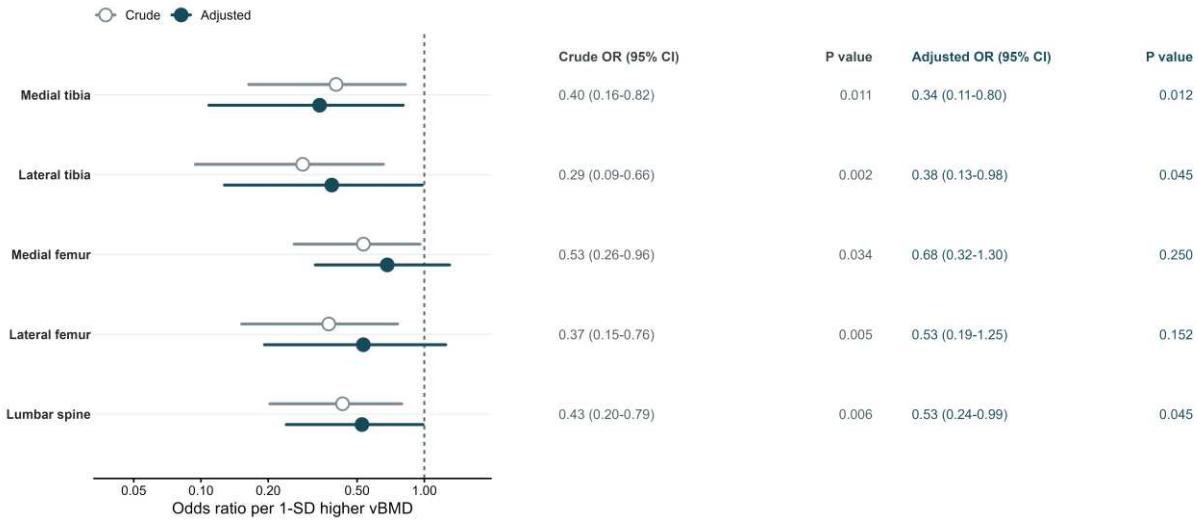


Fig. 3. Unadjusted and adjusted associations between regional vBMD and clinical KOA

Odds ratios (ORs) were estimated using Firth penalised-likelihood logistic regression and reported per one standard deviation (SD) increase in vBMD, using the corresponding SD from non-KOA controls. Adjusted models included age, sex, and BMI. Open grey circles and filled dark-blue circles represent unadjusted and adjusted ORs, respectively; horizontal lines indicate 95% confidence intervals (CIs), and the dashed line marks OR = 1.

TM vBMD was higher than TL vBMD in the KOA group

We next examined medial–lateral vBMD distribution at the tibial plateau and femoral condyles. Figure 4a shows paired medial and lateral vBMD measurements for individual participants. In non-KOA controls, TM and TL vBMD were similar (112.9 vs 115.5 mg/cm³, P = 0.903), whereas TM vBMD was higher than TL vBMD in the KOA group (102.6 vs 77.6 mg/cm³, P = 0.015). At the femoral condyles, FL vBMD was higher than FM vBMD in both non-KOA controls (P = 0.007) and the KOA group (P = 0.005). However, the group × compartment interaction for tibial plateau vBMD was not statistically significant (P = 0.259).

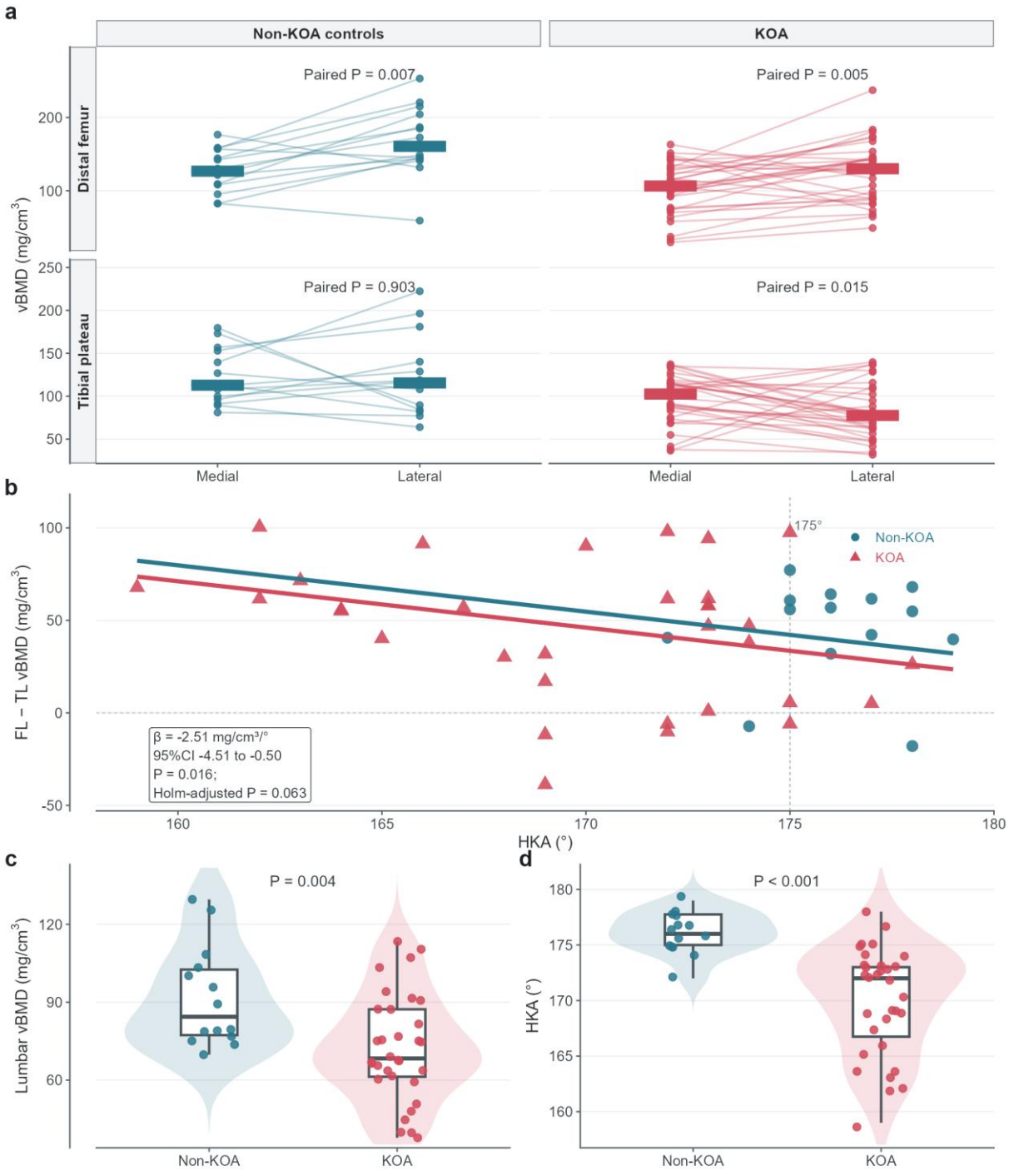


Fig. 4. Regional vBMD distribution and lower-limb alignment in the KOA and non-KOA control groups

(a) Paired comparisons of medial and lateral vBMD at the distal femur and tibial plateau within individual participants. Points and connecting lines represent paired measurements from individual participants, thick horizontal bars indicate medians, and P values were obtained using paired Wilcoxon signed-rank tests. (b) Association between HKA and the FL − TL vBMD difference. Solid lines show group-specific fitted lines. The regression coefficient (β) and its 95%

confidence interval (CI) were estimated using a linear regression model adjusted for KOA status, age, sex, and BMI. Dashed lines indicate HKA = 175° and FL − TL = 0.(c, d) Distributions of lumbar spine vBMD and HKA in the two groups. Violin plots show the data distributions, box plots indicate interquartile ranges, and points represent individual observations.

The lateral femorotibial vBMD difference increased with greater varus alignment

To examine the relationship between lower-limb alignment and regional knee vBMD, we assessed associations between HKA and two medial–lateral tibial measures and four femorotibial vBMD differences. Among all 46 participants, HKA was not significantly correlated with the TM/TL ratio (Spearman's $\rho = -0.257$, $P = 0.085$) or TM − TL ($\rho = -0.224$, $P = 0.135$). Among the four femorotibial differences, FL − TL showed the strongest nominal association with HKA. After adjustment for KOA status, age, sex, and BMI, each 1° increase in HKA was associated with a 2.51 mg/cm³ decrease in FL − TL ($\beta = -2.51$ mg/cm³/°; HC3 robust 95% CI, −4.51 to −0.50; nominal $P = 0.016$) (Fig. 4b). However, this association did not remain statistically significant after Holm correction (adjusted $P = 0.063$). Holm-adjusted P values for the other three differences (FM − TM, FM − TL, and FL − TM) were all ≥ 0.226.

The KOA group had lower 25(OH)D, higher β-CTX, and a positive correlation between N-MID and β-CTX

To examine differences in bone metabolism between groups, we compared bone metabolism markers and assessed their correlations with QCT phenotypes. Data for all six continuous bone metabolism markers were available for all 46 participants. Median 25(OH)D concentrations were lower in the KOA group than in non-KOA controls (53.67 vs 79.09 nmol/L; $P = 0.004$), whereas median β-CTX concentrations were higher (714.0 vs 441.5 pg/mL; $P = 0.003$). Both differences remained statistically significant after FDR correction across the three primary markers ($q = 0.006$ for both). In separate Firth regression models adjusted for age, sex, and BMI, the odds ratios (ORs) for KOA per 1-SD increase, based on the overall sample distribution, were 0.46 for 25(OH)D (95%

CI, 0.19–0.88; P = 0.019) and 2.97 for β-CTX (95% CI, 1.26–9.15; P = 0.011). Median N-MID was higher in the KOA group (24.05 vs 18.35 ng/mL), but neither the between-group difference (P = 0.056; q = 0.056) nor the adjusted association with KOA (OR = 1.93; 95% CI, 0.85–5.27; P = 0.122) was statistically significant. Between-group P values for ALP, serum calcium, and inorganic phosphate were all ≥ 0.129.

Among the 15 pairwise correlations between the six bone metabolism markers, the strongest was between N-MID and β-CTX (ρ = 0.708; q < 0.001). N-MID was also positively correlated with inorganic phosphate (ρ = 0.398; q = 0.046). Both correlations remained statistically significant after FDR correction. In analyses stratified by clinical group, N-MID and β-CTX were positively correlated in the KOA group (ρ = 0.683; P < 0.001), whereas the correlation did not reach statistical significance in non-KOA controls (ρ = 0.442; P = 0.114) (Fig. 5c).

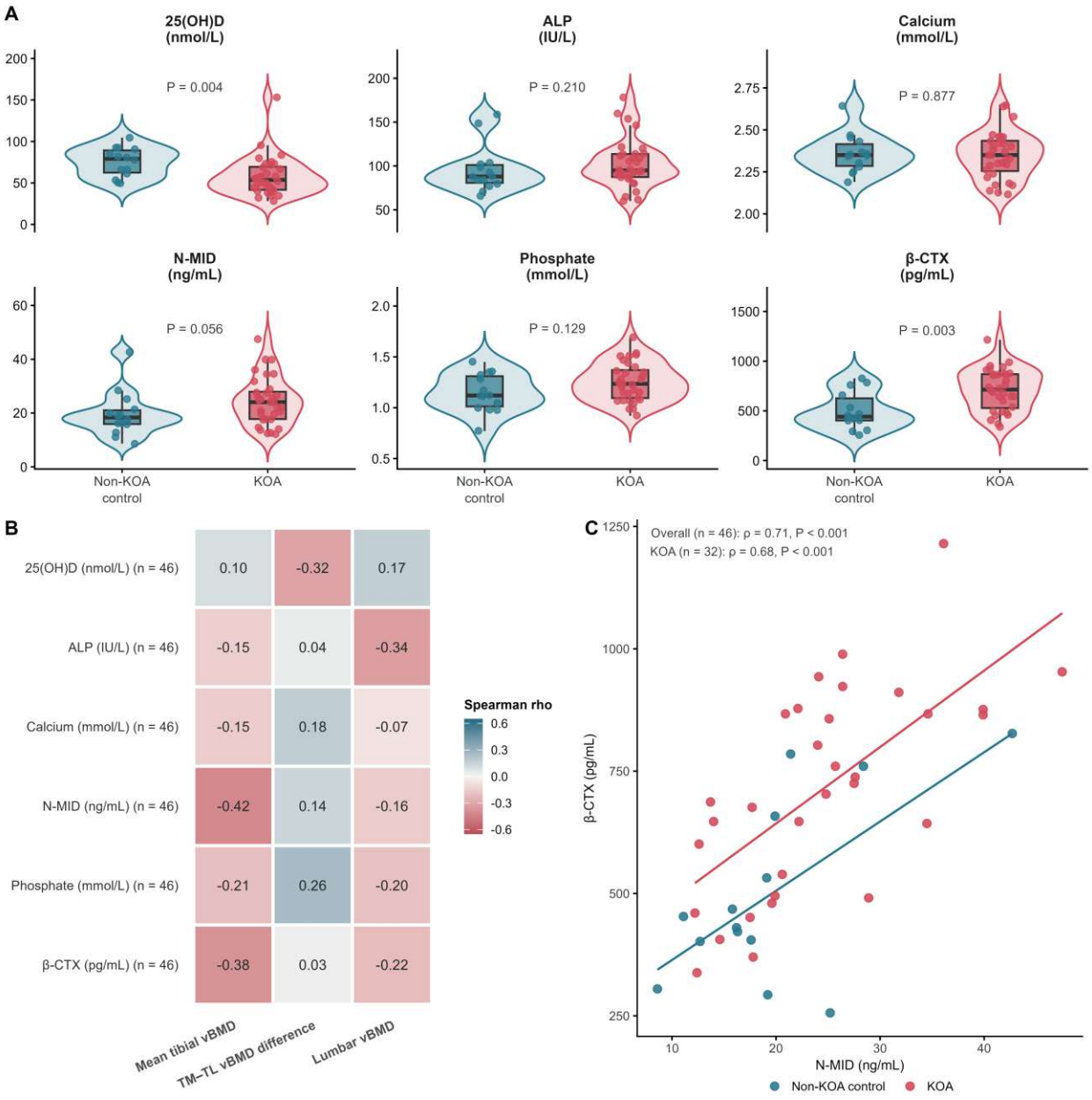


Fig. 5. Bone metabolism markers and QCT phenotypes

(a) Distributions of the six continuous bone metabolism markers in the two groups. (b) Spearman correlations between the six bone metabolism markers and three QCT phenotypes (n = 46); none of the 18 tests remained statistically significant after FDR correction. (c) Scatterplot of N-MID against β-CTX. The two markers were positively correlated in the full sample ($\rho = 0.71$) and within the KOA group ($\rho = 0.68$) (both $P < 0.001$).

Discussion

Osteoarthritis and osteoporosis have long been regarded as diseases with distinct, or even opposing, skeletal phenotypes [7, 10]. With growing recognition of the role of subchondral bone

302 remodelling in structural progression and pain in KOA, this traditional view has increasingly been
303 questioned [3, 4, 6]. However, previous studies have differed in the bone compartments examined,
304 anatomical sites assessed, and measurement techniques used, leaving it unclear whether KOA-
305 associated reductions in bone density are confined to the affected joint or are accompanied by
306 changes at extra-articular sites such as the lumbar spine. In the present study, we measured
307 subchondral trabecular vBMD at the knee and trabecular vBMD at the lumbar spine in the same
308 cohort. The associations between trabecular vBMD and KOA varied by anatomical region: after
309 adjustment for age, sex, and BMI, lower vBMD was associated with KOA at both the medial and
310 lateral tibial plateaus and the lumbar spine, whereas the associations at the femoral condyles were
311 not statistically significant. The finding of lower lumbar vBMD alongside lower tibial plateau
312 vBMD indicates that differences in trabecular bone mass associated with KOA are not confined to
313 the affected knee.
314 Within the knee, the regional pattern of vBMD alterations differed between the tibial plateaus and
315 femoral condyles. Lower vBMD at both the medial and lateral tibial plateaus was associated with
316 KOA after adjustment, whereas neither femoral condyle showed a statistically significant adjusted
317 association. Omoumi et al. compared knees with severe medial-compartment OA with knees
318 without radiographic OA and found lower BMD only in the lateral tibia when the entire weight-
319 bearing region was assessed. This pattern resembles the more pronounced reduction at the lateral
320 tibial plateau in our cohort. Their subregional analysis, however, identified higher BMD in certain
321 medial femoral and tibial regions, in contrast to the lower vBMD observed at both tibial plateaus
322 in our study [23]. Using HR-pQCT, Shiraishi et al. showed that proximal tibial vBMD and
323 trabecular microarchitecture varied across plateaus and subregions [11]. Heiss et al. further
324 demonstrated that knee BMD varied with depth beneath the articular surface and with meniscal

coverage or extrusion, and reported lower BMD in selected medial femoral regions in patients with structural OA [13]. Xu et al. similarly found that associations between BMD and knee pain differed by medial–lateral location and subchondral measurement depth [12]. Using CT, Nielsen et al. also linked knee morphology to subchondral bone attenuation and marginal cortical thickness [24]. These studies are consistent with the spatial heterogeneity observed in our cohort, although the direction of regional bone density differences has varied across studies. Differences in disease stage, ROI location and depth, and the local loading environment associated with meniscal coverage may help explain these findings. Subchondral remodelling may therefore differ between the femur and tibia, making anatomical location and measurement depth essential considerations when interpreting bone changes in KOA.

Within the tibial plateau, medial vBMD was higher than lateral vBMD in the KOA group, although the group-by-compartment interaction was not statistically significant. The medial and lateral tibial plateaus are subjected to different mechanical loads, and coronal lower-limb alignment plays an important role in their distribution. HKA may therefore contribute to the regional vBMD pattern observed in our study. Lo et al. reported quantitative associations between knee alignment and periarticular bone morphology and density, with stronger associations in patients with OA [16]. Han et al. further demonstrated that HKA and tibial plateau compartment jointly influenced subchondral trabecular architecture and bone remodelling [18, 19], while Renault et al. found associations between alignment and medial–lateral differences in tibial microarchitecture and micromechanical properties [25]. Zeng et al. reported more pronounced subchondral microdamage and micromechanical alterations in patients with varus KOA and concomitant osteoporosis [26]. Together, these studies support a relationship between coronal alignment, medial–lateral load distribution, and regional subchondral bone adaptation. In our cohort, the correlations of HKA

with the TM/TL ratio and TM − TL difference were weak and did not reach statistical significance, although their directions were consistent with this mechanical interpretation. Among the femorotibial vBMD differences, FL − TL showed the strongest nominal association with HKA, but this association did not remain statistically significant after correction for multiple comparisons. Compared with studies of advanced OA or specimens obtained at total knee arthroplasty, our in vivo QCT analysis assessed mean trabecular vBMD within relatively large ROIs, capturing bone characteristics at a different spatial scale. Alignment-related remodelling may therefore involve not only differences between the medial and lateral tibial plateaus but also variations in trabecular bone mass between the femur and tibia across opposing articular surfaces. The lower trabecular vBMD observed in this study is not necessarily inconsistent with the subchondral sclerosis commonly seen on knee radiographs in KOA, as these findings reflect different aspects of bone structure. Radiographic subchondral sclerosis is a structural feature seen on two-dimensional projections, whereas dual-energy X-ray absorptiometry (DXA) measures areal BMD without distinguishing between cortical and trabecular bone. In contrast, QCT measures trabecular vBMD within a defined ROI and can identify regional reductions in bone density that may be obscured by projection effects or averaging across larger regions [27]. In our study, knee ROIs were positioned beneath the subchondral plate, excluding the plate itself and the surrounding cortical bone. These measurements therefore reflect the underlying trabecular compartment, where lower vBMD may coexist with radiographic subchondral sclerosis. By using QCT at both the knee and lumbar spine, we could assess trabecular vBMD at both sites on a common volumetric scale and examine whether regional bone differences within the knee were accompanied by altered bone mass at an extra-articular skeletal site.

Extending the analysis to the lumbar spine revealed a pattern that could not readily be explained by local knee mechanics alone. Lower vBMD at both tibial plateaus was accompanied by lower lumbar trabecular vBMD, whereas the femoral condyles showed no statistically significant adjusted associations. Because the lumbar spine is not directly subjected to the local redistribution of joint loading associated with varus knee alignment, the lower lumbar vBMD suggests that bone alterations associated with KOA extend beyond local subchondral remodelling. Previous studies provide relevant evidence. A meta-analysis by Kim et al. showed that OA and osteoporosis are not mutually exclusive and may coexist [7]. Tönük et al. reported an association between lumbar spine BMD and tibiofemoral subchondral cyst burden in postmenopausal women with KOA [28], while Zhang et al. found an association between systemic bone status and varus knee alignment [29]. More recently, Guo et al. reported lower BMD at the distal femur, proximal tibia, and patella in postmenopausal women with KOA and DXA-defined osteoporosis than in those with KOA alone [30]. Although these studies examined different aspects of systemic bone mass, local joint structure, and lower-limb alignment, they suggest that skeletal changes associated with KOA may involve factors beyond local joint mechanics. In our study, QCT was used to assess trabecular vBMD at both the knee and lumbar spine in the same participants during the same study period, allowing measurements at both sites to be made using a common volumetric technique. The observed pattern may therefore reflect two concurrent influences: load-related regional remodelling within the knee and broader skeletal characteristics. Together, these influences may contribute to the variation in trabecular vBMD across anatomical sites.

The serum marker findings provide a metabolic perspective on the extra-articular skeletal changes observed in this study. Patients with KOA had lower 25(OH)D and higher β-CTX levels, and N-MID was strongly correlated with β-CTX. N-MID reflects bone formation-related activity,

whereas β-CTX reflects bone resorption. Their strong correlation is consistent with physiological coupling during bone remodelling. Current consensus recommends β-CTX as a reference marker of bone resorption [21]. The higher β-CTX levels in the KOA group are also consistent with greater bone resorptive activity. Meta-analyses have reported both a high prevalence of vitamin D deficiency among patients with KOA and lower circulating vitamin D levels than in controls [31, 32]. Studies using data from the Osteoarthritis Initiative and other clinical populations have also linked 25(OH)D to knee pain, inflammation, and clinical symptoms [33, 34], although evidence regarding structural outcomes and the benefits of vitamin D supplementation remains inconsistent [35–38]. The lower 25(OH)D levels observed in our cohort are broadly consistent with these reports, but serum bone metabolism markers did not show consistent associations with regional QCT phenotypes. These measures reflect different aspects of bone status: circulating bone turnover markers reflect systemic remodelling activity, whereas QCT measures bone density within specific anatomical regions, reflecting the cumulative effects of bone remodelling over time. Together, lower 25(OH)D, higher β-CTX, and lower trabecular vBMD at the lumbar spine and tibial plateau place the local structural changes associated with KOA within a broader metabolic context.

By assessing regional knee vBMD, lumbar trabecular vBMD, lower-limb alignment, and bone metabolism markers in the same participants during the same assessment period, we were able to examine local bone differences alongside broader skeletal and metabolic features. The study has three main limitations. First, the relatively small sample from a single centre limited the precision of the estimates and the scope for further stratified analyses of alignment and regional imaging features. Second, the cross-sectional design could not establish whether differences in regional vBMD preceded or followed the development and progression of KOA. Third, the QCT ROIs provided mean trabecular vBMD within predefined anatomical regions but did not capture changes

in the subchondral plate, depth-specific bone compartments, or trabecular microarchitecture. Future longitudinal studies with larger samples and a wider range of lower-limb alignment could combine serial QCT measurements, HKA, and bone turnover markers with pain, structural progression, and other clinical outcomes to clarify how regional bone phenotypes evolve and assess their potential for identifying patients at risk of KOA progression or low bone mass [39].

Conclusions

In this cohort, KOA was associated with lower trabecular vBMD at both tibial plateaus and the lumbar spine after adjustment for age, sex, and BMI. The lumbar finding indicates that these bone differences extend beyond the affected knee. Within the KOA group, medial tibial plateau vBMD was higher than lateral tibial plateau vBMD, although the medial–lateral pattern did not differ significantly between groups. Patients with KOA also had lower 25(OH)D and higher β-CTX levels, indicating that regional differences in trabecular vBMD occurred alongside differences in bone metabolism.

Abbreviations

Abbreviation	Definition
25(OH)D	25-hydroxyvitamin D
ALP	alkaline phosphatase
BMD	bone mineral density
BMI	body mass index
β-CTX	β-C-terminal telopeptide of type I collagen
CI	confidence interval
CT	computed tomography
DXA	dual-energy X-ray absorptiometry
FDR	false discovery rate
FL	lateral femoral condyle
FM	medial femoral condyle
HKA	hip–knee–ankle angle
HR-pQCT	high-resolution peripheral quantitative computed tomography
K–L	Kellgren–Lawrence
KOA	knee osteoarthritis
LS	lumbar spine

Abbreviation	Definition
N-MID	N-terminal midfragment of osteocalcin
OA	osteoarthritis
OR	odds ratio
PACS	picture archiving and communication system
QCT	quantitative computed tomography
ROI	region of interest
SD	standard deviation
TL	lateral tibial plateau
TM	medial tibial plateau
vBMD	volumetric bone mineral density

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Kunming Medical University (approval no. (2025) Ethics Review L No. 58 , dated 11 March 2025) and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Consent for publication

Written informed consent for publication of de-identified images and data was obtained from all participants..

Availability of data and materials

The data generated and analysed during this study are not publicly available because they contain sensitive patient information and their public sharing was not covered by the participants' informed consent or the institutional ethics approval. De-identified data may be available from the corresponding author upon reasonable request, subject to approval by the institutional ethics committee and applicable data-protection requirements.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HZ and WW conceived the study and developed the methodology. HZ, XBZ, and XHZ conducted the investigation. HZ and XBZ curated the data. HZ performed the formal analysis, prepared the visualisations, and drafted the manuscript. All authors reviewed and edited the manuscript. WW supervised and administered the project. All authors read and approved the final manuscript.

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