Cross-sectional and longitudinal associations between systemic, subchondral bone mineral density and knee cartilage thickness in older adults with or without radiographic osteoarthritis

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Abstract

Objectives: To investigate cross-sectional and longitudinal associations between systemic bone mineral density (BMD), subchondral BMD (sBMD) and knee cartilage thickness in older adults with or without radiographic osteoarthritis (ROA).

Methods: A prospective cohort of 158 randomly selected subjects (mean 63 years, 48% female) including 69 non-ROA and 89 ROA subjects were studied at baseline and 2.7 years later. Knee cartilage thickness was semi-automatically determined from T1-weighted fat suppressed magnetic resonance imaging (MRI). Knee cartilage volume was measured from MRI. Systemic BMD, and sBMD were measured by dual energy x-ray absorptiometry (DXA).

Results: Cross-sectionally, total body, total hip, spine BMD and/or lateral tibial sBMD were significantly and positively associated with femoral, lateral tibial and/or patellar cartilage thickness in subjects with ROA after adjustment for potential confounders. Longitudinally, a high total body BMD was associated with an increased femoral cartilage thickness (β: 0.33 mm per g/cm^2, 95% CI: 0.13, 0.53), a high spine BMD was associated with an increased femoral and lateral tibial cartilage thickness (β: 0.25 mm per g/cm^2, 95% CI: 0.10, 0.41; and β: 0.18 mm per g/cm^2, 95% CI: 0.01, 0.34, respectively), and a high medial tibial sBMD was associated with an increased medial tibial cartilage thickness (β: 0.44 mm per g/cm^2, 95% CI: 0.01, 0.86) in subjects with ROA. In contrast, there were no significant associations between baseline systemic BMD, sBMD and cartilage volume loss, nor were associations between BMD and cartilage thickness in subjects without ROA.

Conclusions: Both systemic and subchondral BMD are positively associated with increased cartilage thickness in subjects with ROA, suggesting BMD may play a protective role against cartilage loss in knee OA.

INTRODUCTION

Osteoarthritis (OA) is a slowly progressive and multifactorial disease characterised by gradual loss of articular cartilage.(1) It has long been hypothesised that systemic or local bone mineral density (BMD) is involved in the pathogenesis of cartilage degradation;(2-4) however, studies regarding the association between BMD and incidence or progression of OA are still controversial.

While some studies demonstrated that high systemic BMD and BMD gain decreased the risk of progression of knee radiographic OA (ROA) or osteophyte progression,(5, 6) others reported that high BMD in women was associated with incident ROA,(6, 7) or was not related to hip osteophyte formation.(8) A recent study with large sample size documented that higher systemic BMD was associated with a greater risk of incident ROA, but not the progression of existing ROA.(9) Subchondral BMD (sBMD) and subchondral bone remodelling also play important roles in OA pathology.(10, 11) Some studies have demonstrated that knee OA was associated with lowers BMD,(3, 12) while another study documented that patients with high tibial sBMD had increased joint space narrowing (JSN) over 1 year.(13)

These inconsistencies may be partly due to the radiographic assessment of OA incidence or progression being insensitive. JSN assessed by radiographs only provides an indirect estimateof cartilage loss and is subject to measurement errors due to change in positioning. Cartilage thickness assessed from magnetic resonance imaging (MRI) as a potential morphologic biomarker of OA has been recommended by an international panel of experts and has been recognised as an important quantitative measurement of knee osteoarthritic status.(14,

15) While Raynauld et al reported that measurements of both cartilage thickness and cartilage volume provided the same level of sensitivity to estimate cartilage loss in patients with symptomatic OA (16), Reichenbach et al suggested that reduced knee cartilage thickness rather than volume was observed in subjects with mild to moderate ROA compared with those without radiographic OA. (17) Both loss of cartilage volume and loss of cartilage thickness can predict future knee replacement.(17, 18) Although some studies reported that systemic BMD was cross-sectionally associated with increased knee cartilage volume,(19-21) the associations between systemic and/or subchondral BMD and knee cartilage thickness have not been reported. It is also unclear if systemic BMD and sBMD play different roles in cartilage loss over the process of OA. The aim of this study, therefore, was to determine the cross-sectional and longitudinal associations between systemic BMD, subchondral BMD and knee cartilage thickness in older adults with or without ROA.

MATERIALS AND METHODS

Study design and subjects

This study was conducted as part of the Tasmanian Older Adult Cohort (TASOAC) study, a prospective epidemiological study of 1100 persons aged 50–79 years, with a goal of identifying the environmental, genetic and biochemical factors associated with the development and progression of OA and osteoporosis (the overall response rate was 57%). Participants were selected randomly using computer generated random numbers from the electoral roll in southern Tasmania (population 229,000), a comprehensive population listing, with an equal number of men and women. Institutionalised persons were excluded. The study was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee, and written informed consent was obtained from all participants. Self-report of smoking status and disease status such as rheumatoid arthritis (RA), asthma, cardiovascular disease and diabetes

were recorded by questionnaire as such disease status may be potential confounders for bone or cartilage metabolism. Baseline measurements were carried out from April 2002 to September 2004 with a predefined time point for each participant, and the first follow up was conducted 2.7 years later (range 2.6-3.3 years).. At baseline and 2.7 years' follow up, all participant received MRI and dual energy x-ray absorptiometry (DXA) scan, while the first 158 participants were selected to perform the semi- automated measurements of cartilage thickness.

Anthropometrics

Height was measured to the nearest 0.1 cm by using a stadiometer with shoes, socks and headgear removed. Weight was measured to the nearest 0.1 kg (with shoes, socks and bulky clothing removed) using a single pair of electronic scales (Seca Delta Model 707, Bradford, Massachusetts, USA) that were calibrated using a known weight at the beginning of each clinic. Body mass index (BMI) [weight (kg)/height^2 (m^2)] was calculated.

BMD measurement

Bone mass was measured using a Hologic DXA scanner (Hologic Corp., Waltham, Massachusetts, USA). Bone mass was examined as areal BMD (g/cm^2), which is calculated by dividing the bone mineral content (BMC) by the area measured and was measured at total hip, lumbar spine and total body at baseline. The precision estimate in vivo is 2% in our hands.(22) By using existing spine software, medial and lateral sBMD of the tibia were measured in regions of interest (ROIs) including the subchondral plate and had a height of 10 mm. Reproducibility and validity in these ROIs have been demonstrated in our previous study.(23, 24)

Knee cartilage thickness measurement

Using a commercial transmit/receive extremity coil, MRI of the right knee was performed at baseline and follow up with a 1.5T whole-body magnetic resonance unit (Picker). The following sequence and parameters were used: a T1-weighted fat suppression 3-dimensional (3-D) gradient-recalled acquisition in the steady state, flip angle 30°, repetition time 31ms, echo time 6.71 ms, field of view 16cm, 60 partitions, 512x512-pixel matrix, acquisition time 5 minutes 58 seconds, 1 acquisition, sagittal images obtained at a partition thickness of 1.5 mm without a between-slice gap.

Segmentation was performed by one of us (OS) using custom semi-automated segmentation software written in MATLAB. The semi-automated approach used the following method. First the user selected start and end sagittal images for each major cartilage region (femoral, medial tibial, lateral tibial and patellar), as well as seed points in the subchondral bone midway between the two slices.(25, 26) Initial boundary finding for the bone–cartilage interface was performed by an active contour approach. The contour was seeded as a thin cylindrical mesh along the sagittal axis and grew outwards, where the user was able to adjust coefficients relating to internal and image forces to find a good fit. After fine adjustment of this inner contour by gray scale smoothing and thresholding, a 2D grayscale image was presented representing the mean signal intensity over several pixels outward from the subchondral bone–cartilage interface. The user was able to delineate the edges (boundary where inner and outer surfaces meet) of the cartilage region. A second active contour projected outwards, controlled by the user, was used to find the outer surface of the cartilage. The final stage involved checking and manual adjustment of contours in individual slices to correct any errors. This method allowed for non-contiguous portions of cartilage to be grouped together, and was sensitive to portions of cartilage unconnected in the same slice.

For our analysis, femoral cartilage was considered as a single region, as was patellar cartilage. Medial and lateral tibial portions of cartilage were considered as separate whole regions.

Analysis was also performed using all knee cartilage combined. Mean thickness for a region of cartilage was calculated as the mean distance from inner to outer surface, from a sample of uniformly spaced points over the entire cartilage-covered surface. Intra-observer reproducibility (measured in 20 subjects) for mean cartilage thickness, as measured by coefficient of variation (CV), was 1.9-2.9%. This is similar to that for cartilage volume in our hands. (27)

Knee cartilage volume and bone marrow lesion measurements

Knee cartilage volume and bone marrow lesions (BMLs) were determined by means of image processing on an independent work station as previously described. (27, 28) (Please add a ref for BMLs)

Radiographic OA and knee pain assessment

According to the Osteoarthritis Research Society International (OARSI) atlas (29) and as our previously reported,(28) a standing anteroposterior semiflexed view of the right knee with 15º of fixed knee flexion was performed in all subjects at baseline and scored individually for JSN and osteophytes on a scale of 0–3 (0=normal and 3=severe). Medial or lateral JSN was scored separately, while osteophytes were scored at each site of medal tibia, medial femur, lateral tibia and lateral femur. The presence of ROA was defined as any JSN or osteophyte score of ≥ 1 in individual compartment.

Each component of knee pain (on a flat surface, going up/down stairs, at night, sitting/lying, and standing upright) at baseline was assessed by self-administered Western Ontario McMaster Osteoarthritis Index (WOMAC) questionnaire (30) with a 10-point scale from 0 (no pain) to 9 (most severe pain). Total knee pain was summed all component to create a total pain (0 to 45) score.

Data analysis

Change in cartilage thickness was calculated by subtracting the baseline level from the follow up level divided by the interval between measures. Rates of change in cartilage volume were calculated as: percentage change per annum = [100*((follow-up volume - baseline volume)/ baseline volume)/ time between two scans in years].

Student t- or χ^2 tests were used to compare means or proportions, respectively. Univariable and multivariable linear regression analyses were used to examine the associations between baseline BMD and both baseline and change in knee cartilage thickness, before and after adjustment for age, sex, BMI, smoking status, radiographic features if ROA subjects, BMLs if sBMD as the independent variable and disease status (RA, cardiovascular disease, asthma and diabetes). Standard diagnostic checks of model fit and residuals were routinely made, and data points with large residuals and/or high influence were investigated for data errors.

Interactions between ROA (or sex) and BMD were investigated by testing the statistical significance of the coefficient of a product term (ROA or sex × BMD) after adjustment for confounders. A p value <0.05 (two-tailed) or a 95% confidence interval not including the null point (for linear regression) was regarded as statistically significant. All statistical analyses were performed on SPSS V20.0 for Windows (SPSS, Chicago, Illinois, USA).

RESULTS

There were no significant differences in demographic factors between the current cohort and the subjects who did not have cartilage thickness measured (data not shown). Of 158 subjects (48.1% female) included in the analysis, the average age at baseline was 62.6 years, and the mean BMI was 27.4kg/m^2. Subjects with (n=89) or without ROA (n=69) were similar in terms of age, gender, BMI, BMD, sBMD at medial tibial site, BMLs, smoking and disease status;

however, subjects with ROA had reduced sBMD at lateral tibial site (p=0.05) and a lower cartilage thickness (P<0.05) except in whole femur site (Table 1). Tibial sBMD was not measured in 19 subjects (4 without ROA, 15 with ROA) at baseline because the tibial DXA films could not be found. There were significant interactions between ROA status and BMD on baseline cartilage or change in cartilage thickness, so subjects with ROA and non-ROA were separated for analyses. There were no significant interactions between sex and BMD on baseline cartilage thickness or change in cartilage thickness, so males and females were combined for analyses.

In cross-sectional analyses of ROA subjects, total body and spine BMD were significantly associated with knee cartilage thickness at whole femoral, whole patellar and lateral tibial sites before and after adjustment for age, sex, BMI, disease status and knee radiographic features (Table 2). Total hip BMD was also significantly associated with femoral, patellar and lateral tibial cartilage thickness in univariable analysis and remained significant at femoral and lateral tibial sites after adjustment for the covariates as mentioned above (Table 2). After further adjustment for medial and/or lateral tibial sBMD, the significant associations decreased in magnitude and became non-significant except those at lateral tibial site (Table 2).

As shown in Table 3, we did not find significant associations between medial sBMD and knee cartilage thickness at any site, but lateral sBMD was significantly associated with femoral and patellar cartilage thickness in multivariable analyses. After further adjustment for total body BMD, the association with femoral cartilage thickness remained significant but decreased in magnitude, and the association with patellar cartilage thickness became non-significant (Table 3).

Longitudinally, in subjects with ROA, a high baseline spine BMD was associated with an increase in cartilage thickness in both femoral and lateral tibial sites, and baseline total body

BMD was positively associated with change in whole femoral cartilage thickness, after adjustment for age, sex, BMI, baseline cartilage thickness, radiographic features and disease status (Table 4). Baseline medial sBMD was also positively associated with change in cartilage thickness in medial tibial site before and after the adjustment in ROA subjects (Table 5). All these significant values in longitudinal data were largely unchanged after further adjustment for sBMD if systemic BMD or total body BMD if sBMD (Table 4, 5).

In non-ROA subjects, before and after adjusting for above confounders, we did not find any significant association between systemic or subchondral BMD and cartilage thickness cross-sectionally and longitudinally (supplementary Tables 1-4), except that total hip BMD was associated with baseline patellar cartilage thickness in univariable analysis (β: 0.75mm per g/cm^2, 95% CI: 0.01, 1.50, P=0.04).

When cartilage volume was used as the outcome measure, we only found significantly positive associations between baseline total body BMD, total hip BMD and baseline patellar cartilage volume in ROA subjects (β: 1098.2, 95% CI: 280.5, 1915.9; β: 703.7, 95%CI: 43.3, 1364.1, respectively) after adjustment for confounders. Longitudinally, we did not find significant associations between baseline systemic BMD, sBMD and cartilage volume loss at any site (data not shown).

DISCUSSION

This is, to the best of our knowledge, the first study to examine the relationship between knee cartilage thickness and systemic or local BMD. In this prospective cohort of older adults, we documented that in subjects with ROA, total body and spine BMD were significantly associated with knee cartilage thickness at whole femoral, whole patellar and lateral tibial sites cross-sectionally; and longitudinally, they were also positively associated with increases in whole femoral or lateral tibial cartilage thickness over 2.7 years. Consistent with systemic

BMD, medial tibial sBMD predicted increased medial tibial cartilage thickness. These suggest a causal relationship between low BMD and loss of cartilage thickness in ROA. We did not find significant associations between BMD and cartilage thickness in subjects without ROA.

It has been a commonly-held belief that OA is more common in subjects with high BMD; (31, 32) however, the role of BMD in progression of ROA is still uncertain. Some studies have documented that higher BMD protects against ROA or JSN progression (5, 6); on the contrary, Bergink found that high systemic BMD at baseline was associated with increased progression of knee ROA, (33) while Nevitt reported that in knees with prevalent ROA, BMD was not associated with progression of JSN. (9) It should be noted that Nevitt's study had a much larger sample size with progressive JSN (more than 100 in each quartile of BMD) than Bergink's study (25 progressor knees in the entire cohort). Both studies used radiographic assessment rather than quantitative cartilage measurement, which may lead to potential measurement error, thus more sensitive and direct assessments of articular cartilage are required.

Assessment of cartilage thickness by MRI, (34) with fat-suppressed gradient echo sequences, and appropriate image analysis techniques, has been used with high accuracy and adequate precision for detecting early cartilage damage (35) in healthy subjects and patients with OA. (36-38) Using this technique, we reported that BMD was positively associated with cartilage thickness and change in cartilage thickness in subjects with ROA, independent of potential confounders including JSN or osteophyte. The results for systemic or local BMD were consistent and partly dependent of each other for cross-sectional associations. The importance of bone changes in the progression of OA is still being debated. Although it has been suggested that increased subchondral bone stiffness increases peak dynamic forces in the overlying articular cartilage and can accelerate its damage overtime, (39, 40) the functional integrity of the articular cartilage depends on not only the mechanical properties of the underlying bone but also subchondral bone turnover which is deemed to be associated with more rapid

progression of knee OA. (41) Therefore, it is rational that sBMD can have a protective effect against cartilage worsening. Indeed, antiresorptive therapy with the effect of elevating BMD significantly decreased MRI-detected subchondral bone attrition, BMLs, (42) and even severity of symptoms. (43) Evidences from randomized controlled trials have documented different drug strategy elevating BMD could reduce the expression of a cartilage degradation marker (44) or could slow radiological and symptomatic progression of OA. (45) Accordingly, modification of subchondral bone mineral content and quality have potentially been a target for therapeutic intervention of OA. (46)

These significant associations did not exist in people without ROA, suggesting higher systemic BMD is protective against cartilage degradation only in ROA. The reasons for this discrepancy are unclear, but change in cartilage thickness is usually more dynamic with greater loss in ROA than non-ROA, (47, 48) and thus would be more susceptible to risk factors such as low BMD in subjects with ROA. Except from that, assessment of effect of the chronic risk factors, such as BMD, on ROA progression among individuals with OA may be susceptible to potential selection bias which is difficult to control.(49)

Preliminary epidemiological studies have reported a positive association between total body BMD and medial and lateral tibial cartilage volume, but not patellar cartilage volume in both men and women.(19, 20) Another study also reported that medial cartilage volume was positively associated with BMD at the spine, total body and femoral neck and Ward's triangle in asymptomatic young to middle-aged females without any clinical signs of OA.(21) As these were cross-sectional studies and conducted in healthy subjects, a temporal relationship between BMD and OA has not yet been demonstrated. We selected cartilage thickness as our primary outcome measure, as loss of cartilage thickness may reflect the change in earlier phases of OA, which would be more appropriate for our cohort selected randomly from the community. We did find significant association between systemic BMD and patellar cartilage volume in

subjects with ROA, but we did not find significant associations between BMD and tibial cartilage volume as well as change in cartilage volume at any site. The reasons for this are unknown, but it may reflect a relatively higher sensitivity of thickness than volume in measuring early cartilage changes. (50) In addition, while cartilage volume is a function of cartilage thickness and the size of the contacting area with subchondral bone, cartilage thickness is a measure independent of tibial bone area. As tibial bone area was associated with increased OA severity (Wluka ARD 2005) and cartilage volume loss (10), and BMD refers to the amount of mineral matter per square centimeter of bone area, tibial bone area may affect to determine the significant association between BMD and cartilage volume loss, even though it was used for adjustment in the regression models. This needs to be verified in further longitudinal studies.

There are a number of potential limitations in this study. First, the response rate at baseline was 57%, possibly due to the demands on study participants in that each visit took 3 hours. This did leave the possibility open for selection bias. However, there were no significant differences in age and gender between those responded and those did not. We also had high rates of retention (82%) to offset this. Second, the sample size was modest. It is possible that with a larger sample we may have been able to detect more significant associations. Third, although we studied a well-characterised population of older adults with a high level of knee pain (46%), this randomly selected sample unavoidably included subjects with other diseases, which may have affected the associations. Nevertheless, the results were largely unchanged when the analyses were adjusted for disease status or the subjects with other diseases were excluded. Fourth, disease status was not confirmed by medical records in this study; however, the results remained largely unchanged before and after adjustment for disease status, suggesting it was not a critical confounder. Last, measurement error may influence results. However, given all measures (e.g., cartilage thicknessand BMD) were highly reproducible, this is considered unlikely.

In summary, while total body, total hip and/or spine BMD is positively associated with increased cartilage thickness cross-sectionally and longitudinally in subjects with ROA, a high medial tibial sBMD predicts an increase in medial tibial cartilage thickness. These suggest that both systemic and subchondral BMD play a protective role against cartilage loss in knee OA.

Table 1. Baseline characteristics of participants

	Total		None ROA		ROA		
	(N=158)		(N=69)		(N=89)		P
Age (years)	62.5	(7.24)	61.9	(6.58)	63.0	(7.71)	0.49
Female Gender	76	(48.1%	30	(43.5%	46	(51.6%	0.31*
BMI (kg/m^2)	27.4	(4.13)	27.1	(3.98)	27.6	(4.26)	0.76
Systemic BMD (g/cm^2)							
Spine	1.02	(0.20)	1.04	(0.17)	1.01	(0.22)	0.34
Total hip	0.98	(0.17)	0.98	(0.16)	0.98	(0.17)	0.97
Total body	1.08	(0.16)	1.10	(0.13)	1.07	(0.18)	0.16
Subchondral BMD							
Medial tibia	0.12	(0.07)	0.11	(0.05)	0.12	(0.08)	0.23
Lateral tibia	0.05	(0.03)	0.05	(0.03)	0.04	(0.02)	0.09
WOMAC total pain	7.9	(5.30)	7.7	(4.70)	8.1	(5.40)	0.59
JSN ≥1							
Medial	80	(50.6%		/	80	(89.9%	
Lateral	24	(15.2%		/	24	(27.0%	
Osteophyte ≥1							
Medial tibial	6	(3.80%		/	6	(6.80%	
Medial femur	5	(3.20%		/	5	(5.70%	
Lateral tibial	4	(2.50%		/	4	(2.30%	
Current smoker	60	(37.9%	23	(33%)	37	(41.5%	0.59*
Any BMLs	67	(42.4%	27	(39.1%	40	(44.9%	0.62*
Cartilage thickness (mm)							
Whole femur	3.29	(0.45)	3.34	(0.47)	3.25	(0.44)	0.29
Whole patellar	4.33	(0.60)	**4.50**	**(0.52)**	**4.20**	**(0.63)**	**<0.00**
Lateral tibial	3.5	(0.45)	**3.58**	**(0.43)**	**3.43**	**(0.47)**	**0.02**
Medial tibial	3.01	(0.37)	**3.10**	**(0.37)**	**2.95**	**(0.35)**	**0.007**

Mean (SD),otherwise count (%) for dichotomous variables. BMI: body mass index; BMLs: bone marrow lesions; JSN: joint space narrowing; ROA: radiographic osteoarthritis; WOMAC: Western Ontario McMaster Osteoarthritis Index. #n=129 with 65 in non-ROA and 74 in ROA.*Ch^2 tests, others t- tests.

Table 2. Associations between systemic BMD and cartilage thickness at baseline in ROA subjects: cross-sectional data

	univariable		*multivariable **		*multivariable***	
	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
Total body BMD						
Femoral cartilage	**0.87 (0.40,1.34)**	**<0.001**	**0.65 (0.14,1.16)**	**0.01**	0.53 (-0.06,1.12)	0.08
Patellar cartilage	**1.29 (0.61,1.97)**	**<0.001**	**0.97 (0.17,1.76)**	**0.02**	0.92 (0,1.84)	0.05
Medial tibial cartilage	**0.42 (0.03,0.82)**	**0.03**	0.32 (-0.11,0.76)	0.14	0.27 (-0.25,0.79)	0.30
Lateral tibial cartilage	**0.84 (0.32,1.36)**	**0.01**	**0.63 (0.11,1.15)**	**0.01**	**0.63 (0.04,1.22)**	**0.04**
Spine BMD						
Femoral cartilage	**0.52(0.11,0.93)**	**0.01**	**0.4(0.04,0.82)**	**0.03**	0.3 (-0.17,0.77)	0.21
Patellar cartilage	**0.74(0.15,1.33)**	**0.01**	**0.69(0.05,1.33)**	**0.03**	0.67 (-0.06,1.40)	0.07
Medial tibial cartilage	0.17(-0.17,0.51)	0.32	0.20(-0.15,0.55)	0.25	0.16 (-0.25,0.56)	0.44
Lateral tibial cartilage	**0.49(0.05,0.93)**	**0.02**	**0.52 (0.10,0.92)**	**0.01**	**0.52 (0.08,0.97)**	**0.02**
Total hip BMD						
Femoral cartilage	**0.81(0.29,1.33)**	**0.01**	**0.69(0.08,1.30)**	**0.02**	0.57 (-0.16,1.31)	0.12
Patellar cartilage	**0.81(0.05,1.57)**	**0.03**	0.72 (-0.31,1.74)	0.16	0.17 (-1,1.34)	0.78
Medial tibial cartilage	0.38(-0.05,0.81)	0.08	0.52 (-0.03,1.06)	0.06	0.57 (-0.05,1.19)	0.07
Lateral tibial cartilage	**0.73(0.17,1.29)**	**0.01**	**0.86(0.20, 1.51)**	**0.01**	**1.01 (0.3,1.71)**	**0.01**

Dependent variable: mean cartilage thickness (mm) in respective compartment at baseline. Independent variable: BMD at baseline. * Adjusted for age, sex, BMI, disease status and/or radiographic features (any medial or lateral joint space narrow or osteophyte). **Further adjusted for medial subchondral BMD if medial tibial cartilage or lateral subchondral BMD if lateral tibial cartilage or medial and lateral subchondral BMD if femoral or patellar cartilage. Data in bold denote a statistically significant results. CI: confidence interval; BMD: bone mineral density; BMI: body mass index; ROA: radiographic osteoarthritis.

Table 3. Associations between subchondral BMD and cartilage thickness at baseline in ROA subjects: cross-sectional data

	univariable		*multivariable **		*multivariable***	
	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
Medial subchondral BMD						
Femoral cartilage	0.93(-0.22,2.08)	0.11	0.62 (-0.69, 1.95)	0.35	0.19 (-1.16,1.56)	0.77
Patellar cartilage	2.42(0.73,4.11)	0.01	1.86 (-0.13, 3.85)	0.06	1.16 (-0.88,3.20)	0.25
Medial tibial cartilage	0.11(-0.85,1.07)	0.82	0.17 (-0.89, 1.25)	0.74	-0.03 (-1.17,1.09)	0.94
Lateral tibial cartilage	0.80(-0.46,2.07)	0.21	0.14 (-1.13, 1.42)	0.81	-0.32 (-1.64,0.97)	0.61
Lateral subchondral BMD						
Femoral cartilage	**5.04(1.19,8.89)**	0.01	**5.62 (1.67, 9.57)**	**0.01**	**4.97 (1.05,8.89)**	**0.01**
Patellar cartilage	**7.35(1.47,13.23)**	0.02	**6.46 (0.18,12.74)**	**0.04**	5.14 (-1.01,11.31)	0.10
Medial tibial cartilage	2.48(-0.77,5.74)	0.13	2.59 (-0.75,5.93)	0.13	2.28 (-1.12,5.68)	0.19
Lateral tibial cartilage	2.47(-1.88,6.82)	0.26	2.97 (-1.01,6.96)	0.14	2.25 (-1.70,6.21)	0.26

Dependent variable: mean cartilage thickness (mm) in respective compartment at baseline. Independent variable: subchondral BMD at baseline. * Adjusted for age, sex, BMI, disease status ,radiographic features (any medial or lateral joint space narrow or osteophyte),and BMLs. **Further adjusted for total body BMD. Data in bold denote a statistically significant results. CI: confidence interval; BMD: bone mineral density; BMI: body mass index; ROA: radiographic osteoarthritis; BMLs: bone marrow lesions.

Table 4. Associations between systemic BMD and change in cartilage thickness in ROA subjects: longitudinal data

	univariable		*multivariable **		*multivariable***	
	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
Total body BMD						
Femoral cartilage	**0.33(0.13,0.52)**	**0.01**	**0.33 (0.13,0.53)**	**0.01**	**0.31(0.08,0.53)**	**0.01**
Patellar cartilage	-0.07(-0.28,0.13)	0.46	0.01 (-0.22,0.24)	0.91	0.07(-0.2,0.34)	0.60
Medial tibial cartilage	0.04(-0.12,0.21)	0.59	0.06 (-0.12,0.25)	0.49	-0.02(-0.23,0.2)	0.88
Lateral tibial cartilage	0.11(-0.06,0.28)	0.21	0.10 (-0.11,0.32)	0.32	0.14(-0.09,0.37)	0.24
Spine BMD						
Femoral cartilage	0.14(-0.03,0.32)	0.11	**0.25 (0.10,0.41)**	**0.01**	**0.21(0.03,0.39)**	**0.02**
Patellar cartilage	-0.02(-0.18,0.13)	0.78	0.09 (-0.09,0.27)	0.32	0.13(-0.08,0.34)	0.21
Medial tibial cartilage	0.05(-0.08,0.19)	0.42	0.06 (-0.08,0.21)	0.41	-0.04(-0.2,0.13)	0.68
Lateral tibial cartilage	0.12(-0.02,0.26)	0.10	**0.18 (0.01,0.34)**	**0.03**	**0.19(0.01,0.37)**	**0.04**
Hip BMD						
Femoral cartilage	0.07(-0.16,0.30)	0.54	0.23 (-0.02,0.49)	0.08	0.16(-0.13,0.45)	0.28
Patellar cartilage	-0.04(-0.24,0.16)	0.67	0.12 (-0.15,0.40)	0.38	0.17(-0.16,0.49)	0.30
Medial tibial cartilage	0.07(-0.11,0.25)	0.43	0.02 (-0.22,0.26)	0.86	-0.13(-0.39,0.14)	0.34
Lateral tibial cartilage	0.05(-0.13,0.24)	0.59	0.22 (-0.04,0.49)	0.09	0.26(-0.03,0.55)	0.07

Dependent variable: change in mean cartilage thickness (mm) in respective compartment over 2.7 years. Independent variable: BMD at baseline. * Adjusted for age, sex, BMI, disease status, baseline thickness and knee radiographic features (any medial or lateral joint space narrow or osteophyte). **Further adjusted for medial subchondral BMD if medial tibial cartilage or lateral subchondral BMD if lateral tibial cartilage or medial and lateral subchondral BMD if femoral or patellar cartilage. Data in bold denotes a statistically significant result. CI: confidence interval; BMD: bone mineral density; BMI: body mass index; ROA: radiographic osteoarthritis.

Table 5. Associations between subchondral BMD and change in cartilage thicknessin ROA subjects: longitudinal data

	univariable		*multivariable **		*multivariable ***	
	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
Medial subchondral BMD						
Femoral cartilage	0.26(-0.27,0.78)	0.33	0.13 (-0.35,0.62)	0.58	-0.07(-0.55,0.41)	0.77
Patellar cartilage	-0.44(-0.91,0.03)	0.07	-0.21 (-0.77,0.34)	0.43	-0.25(-0.84,0.32)	0.38
Medial tibial cartilage	**0.56(0.18,0.93)**	**0.01**	**0.45 (0.02,0.89)**	**0.04**	0.46(0,0.92)	0.05
Lateral tibial cartilage	0.15(-0.25,0.55)	0.45	0.01 (-0.45,0.48)	0.94	-0.08(-0.57,0.41)	0.74
Lateral subchondral BMD						
Femoral cartilage	0.34(-1.47,2.16)	0.71	0.74 (-0.87,2.37)	0.36	0.53(-0.99,2.08)	0.48
Patellar cartilage	-0.21(-1.86,1.44)	0.80	-0.21 (-1.99,1.57)	0.82	-0.23(-2.04,1.57)	0.79
Medial tibial cartilage	1.04(-0.32,2.38)	0.13	0.60 (-0.83,2.04)	0.40	0.55(-0.91,2.02)	0.45
Lateral tibial cartilage	0.56(-0.81,1.93)	0.42	-0.09 (-1.59,1.41)	0.90	-0.21(-1.72,1.30)	0.78

Dependent variable: change in mean cartilage thickness (mm) in respective compartment over 2.7 years. Independent variable: subchondral BMD at baseline. * Adjusted for age, sex, BMI, disease status, baseline thickness ,knee radiographic features (any medial or lateral joint space narrow or osteophyte) and BMLs. **Further adjusted for total body BMD. Data in bold denotes a statistically significant result. CI: confidence interval; BMD: bone mineral density; BMI: body mass index; ROA: radiographic osteoarthritis; BMLs: bone marrow lesions.

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