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Relationships between cartilage thickness and subchondral bone mineral density in non-osteoarthritic and severely osteoarthritic knees: *In vivo* concomitant 3D analysis using CT arthrography

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SUMMARY

Objective: To test whether subchondral bone mineral density (sBMD) and cartilage thickness (CTh) of femoral condyles are correlated in knees without and with severe medial femorotibial osteoarthritis (OA), using a subregional analysis with computerized tomography (CT) arthrography.
Methods: CT arthrograms of 50 non-OA (18 males, 58.7 (interquartile range (IQR) = 6.6 years)) and 50 severe medial OA (24 males, 60.5 (IQR = 10.7) years) knees, were retrospectively analyzed. Bone and cartilage were segmented using custom-designed software, leading to 3D models on which each point of the subchondral surface is given a CTh and sBMD value. The average sBMD and CTh were then calculated for the entire weight-bearing regions as well as specific subregions of interest. Linear bivariate and multivariable analyses were performed to test for relationships between sBMD and CTh (regional and subregional measures, or medial-to-lateral ratios), with confounders of age, gender, femoral bone size and femorotibial angle.
Results: In non-OA knees, the sBMD and CTh medial-to-lateral ratios were positively correlated for the total region and the external and internal subregions ($r \geq 0.341$, $P \leq 0.015$). In OA knees, sBMD and CTh medial-to-lateral ratios were negatively correlated for the total region and the external and central subregions ($r \leq -0.538$, $P < 0.001$). Additional positive/negative relationships in the non-OA/OA knees were observed between sBMD and CTh measures in the medial compartment.
Conclusions: The positive correlation between sBMD and CTh in non-OA knees, and the negative one in OA knees, bring support to the theory of a subchondral bone/cartilage functional unit, which could help to better understand the pathophysiology of OA.

Introduction

For long considered as a disease of cartilage, osteoarthritis (OA) is currently viewed as a disease of the entire joint, where other articular components may play a primary role in the disease pathogenesis[1,2]. It was proposed in particular that subchondral bone, which is the bone located immediately underneath the cartilage surface, could be involved in the initiation and progression of knee OA[3–5]. Indeed, it has been suggested that subchondral bone and cartilage interact as a functional unit[6]. For instance, there is evidence for a biological cross-talk between cartilage and subchondral bone, for nutrition of the articular cartilage by the subchondral bone through vessels bridging the two tissues, as well as for a coupling of bone and cartilage turnover in OA[6–11]. Overall, recent literature suggests that the interaction between cartilage and subchondral bone is more important than initially thought in the pathogenesis of OA[7,12].

Abbreviations: CT, computerized tomography; OA, osteoarthritis; K/L, Kellgren–Lawrence; CTh, cartilage thickness; sBMD, subchondral bone mineral density; IQR, interquartile range.

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However, to date, the exact mechanisms through which bone and cartilage interact remain debated, and it is not known how this interaction is altered with the development of knee OA[7,12–16]. Moreover, most research in the field has so far come from animals and ex vivo studies, and there is a crucial need to obtain *in vivo* data in the human joint[12]. Medical imaging offers new opportunities to non-invasively gain insight in the relationships between bone and cartilage properties *in vivo* in human joints[12]. Specifically, computerized tomography (CT) has recently been successfully used to provide a thorough three-dimensional analysis of the subchondral bone mineral density (sBMD)[17–19]. This is noteworthy because sBMD has been proposed as a potential actor in the pathogenesis of cartilage degeneration[20,21]. So far, dual energy X-ray absorptiometry (DXA) has been the modality most commonly used to quantify bone mineral density, but due to its technical limitations, including its low resolution and projectional nature, DXA does not permit detailed analysis of the bone mineral density along the articular surfaces of the knee joint and consequently is of limited use for the assessment of sBMD[19].

As for cartilage, its thickness has been widely used as a biomarker of cartilage health or disease status[22–25]. CT arthrography, thanks to the high contrast it provides between cartilage and surrounding tissues, and its high spatial resolution, has been established for years as a method of choice to assess cartilage and its thickness (CTh) in various joints[26–29]. Therefore, the ability of CT arthrography to provide quantitative three-dimensional data *in vivo*, on both sBMD and CTh, represents an opportunity to gather data that could help in a better understanding of the cartilage/subchondral bone functional unit, both in non-OA and OA knees. This is all the more important because of the paucity of data on the relationship between bone and cartilage properties. Indeed, a recent systematic review on the relationships among cartilage thickness, gait mechanics and bone mineral density found only one study reporting relationships between bone mineral density and CTh[30,31]. It is worth mentioning that this unique study used DXA, and therefore could not focus on the subchondral bone or perform three-dimensional subregional analyses[31].

In this paper, our primary aim was to test whether sBMD and CTh in regions and subregions of the femoral condyles are correlated in knees without and with severe medial femorotibial OA, and whether the correlations differ in OA vs non-OA knees.

Due to the paucity of data on sBMD in the literature, our secondary aim was to compare sBMD between OA and non-OA knees and to test for correlations between sBMD and knee alignment.

Methods

Population sample

This retrospective cross-sectional study analyzed CT arthrograms of 100 patients (one knee per patient), divided into two groups of non-OA ($n = 50$) and severe medial femorotibial OA ($n = 50$) knees.

Knee examinations were selected randomly from the institution's database over a period of 2 years. Inclusion criteria were: age of 50 years old or above, and CT arthrogram and lateral and postero-anterior weight-bearing radiographs of the knees obtained on the same day. In this institution, patients in whom internal derangement of joints are clinically suspected are commonly referred for a CT arthrogram, due to a relatively limited access to MRI. Therefore, the institution's database contains CT arthrograms for a range of knee conditions, including non-OA and OA knees.

Exclusion criteria based on the analysis of imaging were as follows: sign of previous osteoligamentous injury, previous knee surgery (including knee replacement surgery, ligamentoplasty, cartilage repair procedures or meniscal repair surgery), inflammatory joint disease, articular crystal deposition disease or poor image quality (including low contrast or blur at the cartilage/synovial fluid interface).

The radiographs of the examinations meeting the inclusion/exclusion criteria were read by a musculoskeletal radiologist with 9 years of experience to determine a modified Kellgren–Lawrence (K/L) grade[32], consisting in grading each knee compartment separately, leading to three K/L grades per knee (medial, lateral and patellofemoral). The non-OA group was defined by a K/L grade <2 for all three compartments, while the severe OA group was defined by a K/L grade ≥3 for the medial femorotibial compartment (MFT), and a K/L grade ≤2 for the other two knee compartments. The presence or absence of OA in the rest of the manuscript refers to this radiographic definition of OA.

We furthermore measured the femorotibial angle and the bicondylar femoral diameter on the weight-bearing radiographs as surrogates of the knee mechanical axis angle and femoral bone size, respectively, following previously reported methodology[33,34]. For the femorotibial angle, the greater the value, the greater the varus alignment.

Patient demographic data are reported in Table I. There was no significant difference between non-OA and OA groups for the distribution between genders ($P = 0.22$), age ($P = 0.13$) and femoral bone size ($P = 0.28$). The femorotibial angle was significantly larger in the OA group ($P < 0.001$), indicating that these knees had a more varus alignment.

Table I
Patient demographics

	Non-radiographic OA*	Severe MFT OA†	Comparison of Non-OA and OA groups (*p*-value)
Number (n)	50	50	
Gender (males/females)	18/32	24/26	$P = 0.22$
Age (years)	58.7 [6.6]	60.5 [10.7]	$P = 0.13$
Femoral bone size: biepicondylar femoral diameter (cm)	7.9 [0.9]	8.1 [0.9]	$P = 0.28$
MFT K/L grade = 0 (n)	38		
MFT K/L grade = 1 (n)	12		
MFT K/L grade = 3 (n)		32	
MFT K/L grade = 4 (n)		18	
Femorotibial angle (degrees)	4.4 ± 1.9	7.8 ± 2.8	**$P < 0.001$**

Data are presented as either number, mean ± standard deviation, or median [interquartile range]. Statistical comparisons of the non-OA and OA groups are reported in the most right column, with indication of the statistically significant differences in bold ($P \leq 0.05$).
MFT: medial femorotibial compartment, K/L: Kellgren and Lawrence.
* K/L grades <2 in medial femorotibial, lateral femorotibial and patellofemoral compartments.
† K/L grades ≥3 in medial femorotibial compartment and K/L grades ≤2 in lateral femorotibial and patellofemoral compartments.

This study was approved by the institutional ethical committee, without requirement for informed consent due to the retrospective study design.

CT arthrograms

Intraarticular injection 10 mL of ionic contrast material was performed in each knee following the same fluoroscopy-guided procedure. CT examinations were then acquired with the patient supine, with extension of the knee, on a 40-row detector helical CT scanner (Somatom Definition AS; Siemens Healthcare, Forchheim, Germany), using the following acquisition parameters: tube voltage, 120 kVp; reference tube current–time product, 350 mAs with the application of a dose modulation protocol (Care Dose 4D; Siemens Healthcare); bone convolution kernel (U70u), voxel size of 0.3 × 0.3 × 0.3 mm. The CT acquisitions lasted less than 30 s. The knees were scanned within 15 min after the intraarticular injection to avoid any substantial penetration of contrast material into the bone or cartilage that could have hindered the measurements[35]. The consistency of the measurements over time was guaranteed by the use of a single scanner, same acquisition parameters and an equal quantity of iodine for all the knees. Furthermore, the clinical scanner used in this study underwent frequent mandatory calibrations.

sBMD and CTh measurements

Femoral sBMD and CTh were measured from the CT arthrograms using previously published methods. In brief, femoral bone and cartilage were segmented semi-manually on each CT arthrogram and 3D mesh model of the tissues were reconstructed[36,37]. The osteophytes were excluded from the bone models. Then, an sBMD value was calculated for each subchondral point of the 3D femur models by averaging the CT intensity in the first 3 mm of bone[17,19]. A penetration of 3 mm was selected to strictly measure the BMD of the subchondral bone[17,38,39]. A CTh value was also determined for each subchondral point of the 3D femur models by calculating the distance to the articular surface of the 3D cartilage models[36,40]. Finally, regional and subregional measures were performed using a common template of the femoral cartilage (Fig. 1)[41,42]. Specifically, the average sBMD and CTh values were calculated over all the points contained in the load-bearing region of the medial and lateral condyles, as well as in three subregions (external, central, internal) of these regions[41,42]. In addition, medial-to-lateral ratios were calculated by dividing the values (sBMD or CTh) in the medial and lateral compartments. Eight knees randomly selected in the non-OA and OA groups were processed (segmentation and regional/subregional measurement) twice by different observers to assess the inter-reader reliability. This evaluation indicated excellent reliability, with intraclass correlation coefficients (ICC) of 0.93 and 0.97 for CTh and sBMD, respectively. All processing was done using custom software implemented with Matlab (R2014b, Mathworks, Natick, MA).

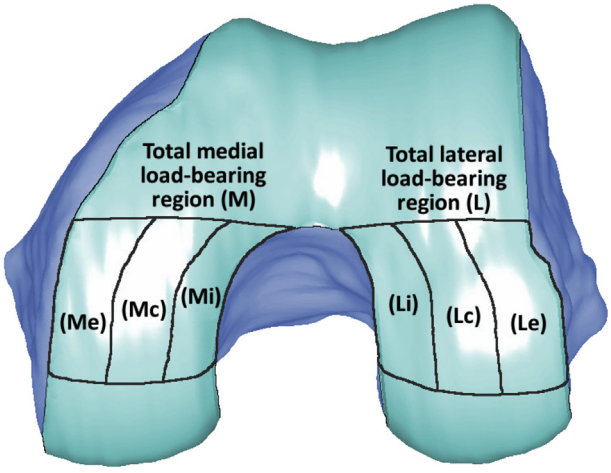

Fig. 1. Diagram representing the standard load-bearing regions of the medial and lateral compartments, as well as the corresponding subregions (external, central, internal) used in this study[41].

Statistical analysis

Regional and subregional sBMD and CTh measures as well as medial-to-lateral sBMD and CTh ratios were compared between the non-OA and OA groups using independent Student's *t*-tests and Cohen's d effect sizes, after confirmation of the normal distribution of the data using Kolmogorov–Smirnov tests. The relationships between sBMD and CTh data were assessed separately for each region, subregion and ratio using linear regressions. First, bivariate analyses were performed using Pearson correlations. Since sBMD and CTh have been associated with age, gender and, body morphology[19,43,44], multivariable regressions were also performed with age, gender, biepicondylar femoral diameter and femorotibial angle as confounders. Specifically, a multivariable model was calculated for each combination of dependent (sBMD measure or ratio) and independent (CTh measure or ratio in the same region or subregion) variables using a backward stepwise regression with forced entry for the four adjustment variables in addition to the independent variable. In these analyses, the rejection threshold was set at $P > 0.1$. Finally, the relationships between the femorotibial angle and each sBMD and CTh measure and ratio were assessed similarly to above, using Pearson correlations and multivariable regressions with age, gender and biepicondylar femoral diameter as confounders.

Statistical analyses were done with SPSS version 23 (IBM, Armonk, NY), considering a significance level of $P = 0.05$ for all tests. The effect size ranges proposed by Cohen were used to describe the strength of the correlations between sBMD and CTh and the strength of differences between non-OA and OA groups[45].

Results

Relationships between sBMD and CTh

In non-OA knees, there were positive relationships of medium to large effect sizes between sBMD and CTh medial-to-lateral ratios for the total load-bearing region and two subregions (Table II). Specifically, the Pearson correlations reported higher sBMD ratios with higher CTh ratios in the total region (M/L: $r = 0.341$, $P = 0.015$), the external subregion (Me/Le: $r = 0.539$, $P < 0.001$), as well as the internal subregion (Mi/Li: $r = 0.373$, $P = 0.008$) (Fig. 2). There was also a positive relationship of medium effect size in the external subregion of the medial compartment (Me: $r = 0.411$, $P = 0.003$). The relationships between sBMD and CTh regional and subregional measures in the lateral compartment were of very small effect sizes ($|r| \leq 0.087$) and statistically non-significant (all $P \geq 0.548$). Adjusting for age, gender, biepicondylar diameter, and femorotibial angle led to the same statistically significant relationships between sBMD and CTh as the bivariate analyses described above. The only differences in multivariable analyses were for the medial-to-lateral ratios in the internal subregion (Mi/Li) and for the measures in the external

Table II
Relationships between femoral subchondral bone mineral density (sBMD) and cartilage thickness (CTh) measures in the medial compartment as well as relationships between sBMD and CTh medial-to-lateral ratios. None of the relationships between sBMD and CTh measures in the lateral compartment was statistically significant (all $P \geq 0.528$, unreported results)

	Non-radiographic OA ($n = 50$)*				Severe MFT OA ($n = 50$)†			
	Bivariate analysis		Multivariable analysis‡		Bivariate analysis		Multivariable analysis‡	
	Standardized β [95% CI]	*P*–value	Standardized β [95% CI]	*P*–value	Standardized β [95% CI]	*P*–value	Standardized β [95% CI]	*P*–value
Medial compartment								
Total (M)	0.058 [−0.23, 0.35]	0.687	§		−0.527 [−0.77, −0.28]	**<0.001**	−0.592 [−0.80, −0.35]	**<0.001**[A]
External (Me)	0.411 [0.15, 0.67]	**0.003**	0.529 [0.24, 0.82]	**<0.001**[g]	−0.559 [−0.80, −0.32]	**<0.001**	−0.470 [−0.71, −0.23]	**<0.001**[M]
Central (Mc)	0.026 [−0.26, 0.31]	0.857	§		−0.509 [−0.76, −0.26]	**<0.001**	−0.583 [−0.82, −0.35]	**<0.001**[A]
Internal (Mi)	0.168 [−0.12, 0.45]	0.242	§		−0.123 [−0.41, 0.16]	0.397	§	
Medial-to-lateral ratio								
Total (M/L)	0.341 [0.07, 0.61]	**0.015**	0.341 [0.07, 0.61]	**0.015**	−0.538 [−0.78, −0.29]	**<0.001**	−0.538 [−0.78, −0.29]	**<0.001**
External (Me/Le)	0.539 [0.29, 0.78]	**<0.001**	0.539 [0.29, 0.78]	**<0.001**	−0.608 [−0.84, −0.38]	**<0.001**	−0.608 [−0.84, −0.38]	**<0.001**
Central (Mc/Lc)	0.199 [−0.08, 0.48]	0.167	§		−0.553 [−0.79, −0.32]	**<0.001**	−0.442 [−0.70, −0.18]	**0.001**[m]
Internal (Mi/Li)	0.373 [0.12, 0.63]	**0.008**	0.409 [0.15, 0.67]	**0.004**[g]	−0.125 [−0.41, 0.16]	0.388	§	

P-values in bold indicate statistically significant relationships between sBMD and CTh variables ($P < 0.05$).
[A/a]: The multivariable model included age in addition to CTh.
[B/b]: The multivariable model included biepicondylar diameter in addition to CTh.
[G/g]: The multivariable model included gender in addition to CTh.
[F/f]: The multivariable model included the femorotibial angle jn addition to CTh.
Uppercase letters: variables included in the model and statistically significant ($P < 0.05$).
Lowercase letters: variables included in the model but not statistically significant ($0.05 \leq P < 0.1$).
* K/L grades <2 in medial femorotibial, lateral femorotibial and patellofemoral compartments.
† K/L grades ≥3 in medial femorotibial compartment and K/L grades ≤2 in lateral femorotibial and patellofemoral compartments.
‡ Backward regression with forced entry for confounders of age, gender, biepicondylar femoral diameter and femorotibial angle.
§ CTh excluded from the model ($P \geq 0.1$).

subregion of the medial compartment (Me), where the effect size of the relationships slightly increased.

In OA knees, three of the four Pearson correlations between sBMD and CTh medial-to-lateral ratios were of large effect sizes: in the total region (M/L: $r = -0.538$, $P < 0.001$), the external subregion (Me/Le: $r = -0.608$, $P < 0.001$) and the central subregion (Mc/Lc: $r = -0.553$, $P < 0.001$) (Table II). But contrary to the results in non-OA knees, these relationships were negative, indicating higher sBMD ratios with lower CTh ratios (Fig. 2). In OA knees, there were also negative relationships of large effect sizes between sBMD and CTh measures in the medial compartment. Specifically, higher sBMD was correlated with lower CTh in the total region (M: $r = -0.527$, $P < 0.001$), the external subregion (Me: $r = -0.559$, $P < 0.001$) and the central subregion (Mc: $r = -0.509$, $P < 0.001$) of the medial compartment. The relationships between sBMD and CTh in the lateral compartment were of very small effect sizes ($|r| \leq 0.091$) and statistically non-significant (all $P \geq 0.528$). Adjusting for confounders of age, gender, biepicondylar diameter and femorotibial angle resulted in the same statistically significant relationships between sBMD and CTh variables as the bivariate analyses aforesaid, with marginal differences in effect sizes.

Comparison of sBMD and CTh between non-OA and OA knees

For the medial compartment, sBMD was higher, in OA than in non-OA knees in the total weight-bearing region, as well as in all subregions (all $P \leq 0.034$), all with large effect sizes except for the internal subregion (small effect size) (Table III). Furthermore, the medial-to-lateral sBMD ratios were higher, with moderate to large effect sizes, in the OA group for both the total weight-bearing region and all its subregions ($P \leq 0.003$).

Medial compartment CTh was lower, with large effect sizes, in OA than in non-OA knees for the total region, as well as all three subregions ($P < 0.001$) (Table III). The medial-to-lateral CTh ratios were lower, with large effect sizes, in the OA group for both the entire region and the three subregions ($P < 0.001$).

Relationships between femorotibial angle and sBMD and CTh variables

In non-OA knees, there was a negative relationship of small effect size between femorotibial angle and sBMD in the internal subregion of the medial compartment (Mi: $r = -0.297$, $P = 0.036$) (Table IV). In OA knees, the femorotibial angle was positively correlated with sBMD in the total region (M), the external subregion (Me) and the central subregion (Mc) of the medial compartment ($r \geq 0.333$, $p \leq 0.018$); all correlations of medium effect sizes. The femorotibial angle was also positively correlated, with medium effect sizes, with sBMD medial-to-lateral ratios in the total region (M/L), the external subregion (Me/Le) and the central subregion (Mc/Lc) ($r \geq 0.386$, $p \leq 0.006$). The positive correlations in OA knees indicated denser bone in the medial compartment and relatively denser bone medially than laterally with larger femorotibial angle (greater varus alignment). The same statistically significant relationships between femorotibial angle and sBMD variables as described above were obtained when adjusting for confounders of age, gender and biepicondylar diameter (unreported results). The effect sizes of the statistically significant relationships were marginally larger in multivariable analyses.

In OA knees, the femorotibial angle was negatively correlated with CTh measures in the medial compartment (M, Me and Mc: $r \leq -0.291$, small to medium effect sizes, $P \leq 0.040$), positively correlated with CTh measures in the lateral compartment (L, Le, Lc and Li: $r \geq 0.329$, medium effect sizes, $P \leq 0.20$), and negatively correlated with the medial-to-lateral CTh ratios (M/L, Me/Le, Mc/Lc and Mi/Li: $r \leq -0.431$, medium effect sizes, $P \leq 0.002$) (Table IV). The correlations in OA knees were consistent, with a larger femorotibial angle (greater varus alignment) associated with absolute and relative thinner medial CTh and thicker lateral CTh. The multivariable analyses led to the same statistically significant relationships between femorotibial angle and CTh (unreported results). Adjusting for age, gender and biepicondylar diameter slightly increased the effect sizes of the statistically significant relationships.

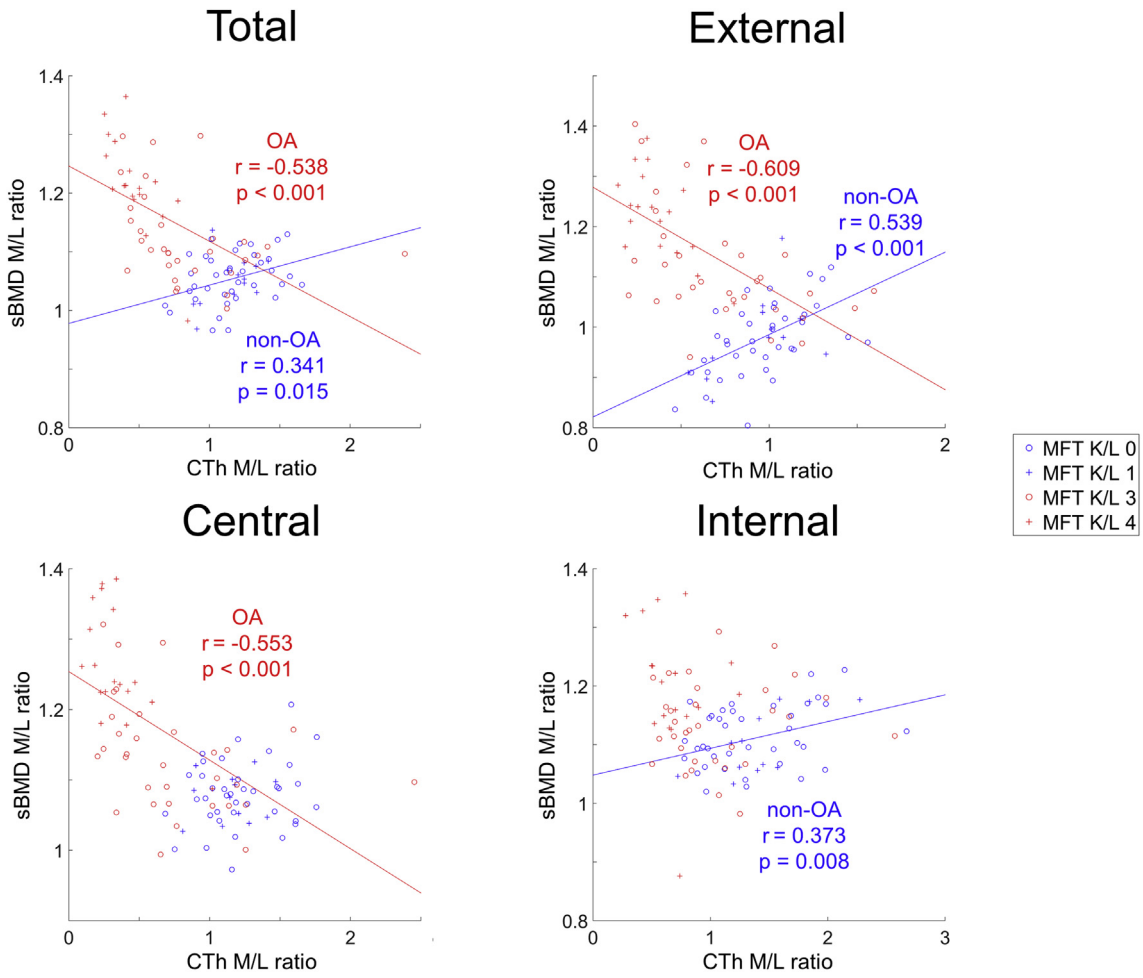

Fig. 2. Scatter plots for the relationships between subchondral bone mineral density (sBMD) medial-to-lateral ratio (sBMD M/L ratio) and cartilage thickness medial-to-lateral ratio (CTh M/L ratio) in the bivariate analysis, for the total region, as well as the external, central and internal subregions. Blue and red symbols correspond to non-OA and OA knees, respectively. The plots also report the Pearson coefficients of correlation (r) and the associated *p*-values in case of statistically significant relationships. To further illustrate the results, the plots differentiate the knees based on the Kellgren and Lawrence grade (K/L) in the medial femorotibial compartment (MFT).

Table III
Comparison of femoral sBMD and CTh between non-OA and OA knees.

	Subchondral bone mineral density (sBMD)			Cartilage Thickness (CTh)		
	Non-radiographic OA* ($n = 50$)*	Severe MFT OA† ($n = 50$)†	P − values	Non-radiographic OA* ($n = 50$)*	Severe MFT OA† ($n = 50$)†	P − values
Medial compartment						
Total (M)	1556.6 ± 61.5	1683.1 ± 126.6	**<0.001**	1.37 ± 0.26	0.82 ± 0.35	**<0.001**
External (Me)	1447.2 ± 96.9	1703.9 ± 174.7	**<0.001**	0.99 ± 0.24	0.63 ± 0.36	**<0.001**
Central (Mc)	1655.7 ± 69.6	1765.5 ± 136.4	**<0.001**	1.88 ± 0.41	0.85 ± 0.52	**<0.001**
Internal (Mi)	1573.5 ± 73.4	1615.8 ± 118.3	**0.034**	1.35 ± 0.30	0.96 ± 0.32	**<0.001**
Lateral compartment						
Total (L)	1478.6 ± 65.7	1458.8 ± 82.1	0.187	1.21 ± 0.27	1.26 ± 0.35	0.470
External (Le)	1483.2 ± 79.4	1474.1 ± 97.2	0.611	1.07 ± 0.27	1.12 ± 0.31	0.459
Central (Lc)	1537.4 ± 75.4	1501.2 ± 92.5	**0.034**	1.60 ± 0.34	1.59 ± 0.50	0.904
Internal (Li)	1417.5 ± 66.9	1399.1 ± 75.0	0.197	1.04 ± 0.28	1.13 ± 0.35	0.142
Medial-to-lateral ratio						
Total (M/L)	1.05 ± 0.04	1.16 ± 0.09	**<0.001**	1.16 ± 0.23	0.70 ± 0.39	**<0.001**
External (Me/Le)	0.98 ± 0.07	1.16 ± 0.12	**<0.001**	0.95 ± 0.25	0.60 ± 0.36	**<0.001**
Central (Mc/Lc)	1.08 ± 0.04	1.18 ± 0.10	**<0.001**	1.21 ± 0.26	0.59 ± 0.45	**<0.001**
Internal (Mi/Li)	1.11 ± 0.05	1.16 ± 0.09	**0.003**	1.38 ± 0.43	0.92 ± 0.44	**<0.001**

Data are sBMD in Hounsfield units and CTh in mm, presented as mean ± standard deviation. *P*-values in bold indicate statistically significant differences between non-OA and OA knees (adjusted $p < 0.05$).

* K/L grades <2 in medial femorotibial, lateral femorotibial and patellofemoral compartments.

† K/L grades ≥3 in medial femorotibial compartment and K/L grades ≤2 in lateral femorotibial and patellofemoral compartments.

Table IV
Pearson correlations between femorotibial angle and bone mineral density (sBMD) and cartilage CTh variables in non-OA and OA knees

	Subchondral bone mineral density (sBMD)				Cartilage Thickness (CTh)			
	Non-radiographic OA* ($n = 50$)*		Severe MFT OA† ($n = 50$)†		Non-radiographic OA* ($n = 50$)*		Severe MFT OA† ($n = 50$)†	
	Standardized β [95% CI]	*P*–value	Standardized β [95% CI]	*P*–value	Standardized β [95% CI]	*P*–value	Standardized β [95% CI]	*P*–value
Medial compartment								
Total (M)	−0.160 [−0.44, 0.12]	0.266	0.333 [0.06, 0.61]	**0.018**	0.074 [−0.21, 0.36]	0.608	−0.297 [−0.57, −0.03]	**0.036**
External (Me)	0.034 [−0.25, 0.32]	0.816	0.443 [0.18, 0.70]	**0.001**	0.111 [−0.17, 0.40]	0.442	−0.291 [−0.56, −0.02]	**0.040**
Central (Mc)	−0.182 [−0.47, 0.10]	0.207	0.355 [0.09, 0.62]	**0.011**	0.112 [−0.18, 0.40]	0.438	−0.329 [−0.60, −0.06]	**0.020**
Internal (Mi)	−0.297 [−0.57, −0.02]	**0.036**	0.102 [−0.19, 0.39]	0.483	−0.010 [−0.30, 0.28]	0.943	−0.162 [−0.44, 0.11]	0.262
Lateral compartment								
Total (L)	−0.075 [−0.36, 0.21]	0.606	−0.099 [−0.39, 0.19]	0.494	0.016 [−0.27, 0.30]	0.910	0.394 [0.13, 0.66]	**0.005**
External (Le)	0.047 [−0.24, 0.34]	0.743	0.026 [−0.26, 0.31]	0.840	0.080 [−0.21, 0.37]	0.583	0.329 [0.05, 0.61]	**0.020**
Central (Lc)	−0.127 [−0.41, 0.16]	0.379	−0.190 [−0.47, 0.09]	0.185	−0.073 [−0.36, 0.21]	0.615	0.335 [0.06, 0.61]	**0.017**
Internal (Li)	−0.181 [−0.46, 0.10]	0.207	−0.153 [−0.44, 0.13]	0.288	0.032 [−0.26, 0.32]	0.823	0.452 [0.20, 0.70]	**0.001**
Medial-to-lateral ratio								
Total (M/L)	−0.073 [−0.35, 0.21]	0.613	0.386 [0.15, 0.63]	**0.006**	0.041 [−0.25, 0.33]	0.775	−0.467 [−0.72, −0.21]	**<0.001**
External (Me/Le)	−0.001 [−0.31, 0.30]	0.996	0.437 [0.16, 0.72]	**0.002**	0.015 [−0.27, 0.30]	0.915	−0.462 [−0.72, −0.20]	**<0.001**
Central (Mc/Lc)	−0.057 [−0.31, 0.20]	0.693	0.446 [0.18, 0.71]	**0.001**	0.203 [−0.07, 0.48]	0.158	−0.443 [−0.70, −0.19]	**0.001**
Internal (Mi/Li)	−0.103 [−0.40, 0.19]	0.478	0.209 [−0.09, 0.50]	0.145	−0.074 [−0.36, 0.21]	0.611	−0.431 [−0.69, −0.17]	**0.002**

P-values in bold indicate statistically significant correlations ($P < 0.05$).
* K/L grades <2 in medial femorotibial, lateral femorotibial and patellofemoral compartments.
† K/L grades ≥3 in medial femorotibial compartment and K/L grades ≤2 in lateral femorotibial and patellofemoral compartments.

Discussion

In this paper, we showed through three-dimensional regional and subregional analyses that sBMD and CTh medial-to-lateral ratios are positively correlated in non-OA knees, and negatively in OA knees, with large effect sizes. These *in vivo* results support the theory of a subchondral bone/cartilage functional unit where the two tissues are adapted to each other in the non-OA knee and where the disease disturbs this homeostatic relationship.

In non-OA knees, the fact that thicker cartilage is positively correlated with denser subchondral bone brings support to the coupling of these two tissues in the healthy state. Although previous animal and *in vitro* studies have pointed to a potential biomechanical and biochemical cross-talk between these tissues, to the best of our knowledge, this is the first report showing the relationship between subchondral bone and cartilage *in vivo* in human knees[7,11,12]. Interestingly, while sBMD and CTh medial-to-lateral ratios were correlated in our study, there was no statistically significant relationship between sBMD and CTh measures in most of the medial or lateral regions/subregions. This observation is in agreement with prior literature where the sensitivity to detect relationships among knee properties was shown to be higher with ratios than with individual measures in the medial or lateral compartments, certainly because ratios allow some normalization of inter-subject variability[42,46].

In OA knees, we have shown that sBMD is negatively correlated with CTh for all regional and subregional measures of the medial compartment, as well as for all medial-to-lateral ratios. In fact, the results showed that while medial cartilage is considerably thinner in severe OA compared to non-OA knees, medial subchondral bone is denser. In severe OA, the adaptation that seems to exist between cartilage and subchondral bone in the healthy state is disturbed. In the latest stages of OA, cartilage destruction and thinning might indeed contribute to the denser subchondral bone in the same compartment by increasing the mechanical load on the latter[7]. The positive correlations between sBMD and CTh in the non-OA knees, contrasting with the negative correlations between these variables in the OA knees are in support of a model of OA pathophysiology based on the disturbances of the homeostatic relationships that exist between variables in the healthy joint[30]. This integrated joint system (IJS) model assumes that the variables are adapted to each other in the non-disease state, just as bone mineral density and cartilage were shown to be correlated positively in non-OA knees. The model then assumes that the disease is initiated when the ability of different variables to adapt to each other is exceeded. Once the disease is established, the positive relationships between variables may be reversed, as illustrated by the negative correlation between sBMD and CTh observed in the OA knees.

The point in the evolution of the disease when this homeostasis is disrupted would be important to determine to improve our understanding of the pathophysiology of OA. One prevailing theory on the pathogenesis of OA is that cartilage degeneration could be related to the density of the subchondral bone: increased stiffness of subchondral bone would increase mechanical constraints on the overlying cartilage and hereby promote cartilage degeneration[20]. However, research aiming at confirming this theory had so far led to conflicting results, most likely due to the lack of methods to specifically study the sBMD[3,31,47]. To further elucidate the exact nature and chronology of events occurring in the subchondral bone of human knees with OA, and their relationships to cartilage degeneration, there is a need to build on the results of our study and assess knees with intermediate OA stages (KL grade 2) using the same technique.

This study builds on previous work showing that sBMD can be assessed tri-dimensionally using CT data[19]. In the current work, we used the ability of CT arthrography to allow simultaneous analysis of sBMD and CTh in high resolution, and in 3D, to assess the correlations between these variables.

The correlation between sBMD and CTh was investigated in non-OA and OA knees in one previous study, but using DXA imaging for sBMD measurement[31]. Among the various pairs of sBMD and CTh measures that were tested cross-sectionally in this previous study, only one reported a statistically significant correlation: in OA knees, higher lateral tibial sBMD was correlated with thicker femoral CTh. The inconsistencies between these previous results and ours may be due to the methods used. Indeed, the portion of the bone considered to quantify sBMD with DXA in this previous study corresponds to a region located further away from the articular surface, which is less relevant to the study of relationships between cartilage and bone properties. Furthermore, DXA imaging is a two-dimensional modality that does not allow any subregional analysis such as in our study. In fact, the many limitations of DXA have led some authors to

suggest that its use in epidemiological research should be restricted[48,49]. The present study also differs from this previous work by analyzing medial-to-lateral ratios in addition to compartmental measures and by testing for correlations between sBMD and CTh data all gathered on the femur. Finally, previous attempts at correlating CTh and other bone parameters exist. For example, Frobell *et al.* found that the differences in total subchondral bone area (tAB) and CTh between pre-radiographic OA and OA knees were weakly correlated[43]. However, the correlations between cartilage and bone parameters were not directly evaluated in the two stages of the disease. Furthermore, while BMD is a widely accepted surrogate of bone metabolic changes, tAB has been less extensively assessed.

Therefore, the main strength of our study is that we could simultaneously analyze sBMD and CTh in non-OA and OA knees using a three-dimensional approach, which to the best of our knowledge, has never been performed so far.

We also aimed to test for correlations between sBMD and knee alignment. In the OA group, femorotibial angle was correlated with greater sBMD in the medial compartment except for one subregion, and with all medial-to-lateral sBMD ratios, except for the internal subregion in the OA population, as expected based on previous reports[44,50]. However, opposite to these previous studies, we did not find any statistically significant correlation in the non-OA knees. This could be due to the differences in methods: because our focus was the subchondral bone-cartilage unit and the correlations between the properties of these tissues, we analyzed BMD immediately below the cartilage. In contrast, previous work has mostly been looking at BMD or other bone parameters further away from the cartilage, where the effects of the mechanical axis of the lower limb may be different.

This study presents several limitations, including its cross-sectional, retrospective design. The relatively small number of patients in each group could be another limitation. The analysis strategy in this study was based on statistical significance and effect size. This conservative strategy could have deemphasized scientifically relevant correlations. Nevertheless, these additional possibly relevant correlations would have probably indicated relationships of similar directionality as the present results, therefore marginally affecting the findings in this study. Moreover, while statistical significance and large effect sizes do not necessarily imply scientific relevance, our findings, in particular the directionality of the correlations, are important and meaningful in light of the current state of knowledge, as discussed above. Furthermore, while we did consider variations in gender, age, bone size and femorotibial angle in the statistical analyses, other potential confounders such as patient weight and body mass index should also be considered in future studies. These data were unfortunately inaccessible in this retrospective study. Another potential limitation is related to the technique used to assess sBMD. Indeed, attenuation measurements by CT could be biased by the non-mineral components of bone (i.e., fat and blood vessels), which are taken into account when measuring the attenuation of each voxel[18]. However, in the first 3 mm of subchondral bone, the influence of non-mineral components of bone is likely negligible compared to its mineral components that largely predominate. Finally, we performed the analyses on the femurs only, and future work should confirm our results on the tibia as well.

In conclusion, we have shown through concomitant regional and subregional analyses of sBMD and CTh that these properties are positively correlated in non-OA knees, and negatively in OA knees. These results obtained *in vivo* bring support to the theory of a cartilage/subchondral bone unit, with an adaptation of the tissues to each other and to their environment in the healthy state, and a loss of this adaptation in the pathological state. Future studies using this technique, notably with intermediate OA stages, could help gain a better understanding of the relationships between subchondral bone and cartilage, which could not only lead to better comprehend the pathophysiology of OA, but also to design novel therapeutic pathways that might be more efficient by targeting a regulation of the common metabolic activity of bone and cartilage[7].

Contributions

Patrick Omoumi and Julien Favre made substantial contributions to all of the following: conception and design; acquisition of data; analysis and interpretation of the data; drafting of the article; critical revision of the article for important intellectual content; final approval of the article; provision of study materials or patients; statistical expertise; obtaining of funding, administrative, technical, or logistic support; collection and assembly of data.

Brigitte M. Jolles made substantial contributions to: acquisition of data; critical revision of the article for important intellectual content; final approval of the article; provision of study materials or patients; obtaining of funding, administrative, technical, or logistic support.

Julien Favre and Brigitte M. Jolles made equal contributions to this work. Hugo Babel made substantial contributions to: analysis and interpretation of the data; statistical expertise; drafting of the article; final approval of the article.

Competing Interests

None.

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References

1. Abramson SB, Attur M. Developments in the scientific understanding of osteoarthritis. Arthritis Res Ther 2009;11:227.
2. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum 2012;64:1697–707.
3. Bruyere O, Dardenne C, Lejeune E, Zegels B, Pahaut A, Richy F, *et al.* Subchondral tibial bone mineral density predicts future joint space narrowing at the medial femoro-tibial compartment in patients with knee osteoarthritis. Bone 2003;32:541–5.
4. Hayami T, Pickarski M, Wesolowski GA, McLane J, Bone A, Destefano J, *et al.* The role of subchondral bone remodeling in osteoarthritis: reduction of cartilage degeneration and prevention of osteophyte formation by alendronate in the rat anterior cruciate ligament transection model. Arthritis Rheum 2004;50:1193–206.
5. Funck-Brentano T, Cohen-Solal M. Subchondral bone and osteoarthritis. Curr Opin Rheumatol 2015;27:420–6.
6. Imhof H, Sulzbacher I, Grampp S, Czerny C, Youssefzadeh S, Kainberger F. Subchondral bone and cartilage disease: a rediscovered functional unit. Invest Radiol 2000;35:581–8.
7. Karsdal MA, Bay-Jensen AC, Lories RJ, Abramson S, Spector T, Pastoureau P, *et al.* The coupling of bone and cartilage turnover in osteoarthritis: opportunities for bone antiresorptives and

anabolics as potential treatments? Ann Rheum Dis 2014;73:336–48.
8. Lajeunesse D, Reboul P. Subchondral bone in osteoarthritis: a biologic link with articular cartilage leading to abnormal remodeling. Curr Opin Rheumatol 2003;15:628–33.
9. Malinin T, Ouellette EA. Articular cartilage nutrition is mediated by subchondral bone: a long-term autograft study in baboons. Osteoarthritis Cartilage 2000;8:483–91.
10. Suri S, Gill SE, Massena de Camin S, Wilson D, McWilliams DF, Walsh DA. Neurovascular invasion at the osteochondral junction and in osteophytes in osteoarthritis. Ann Rheum Dis 2007;66:1423–8.
11. Bay-Jensen A-C, Hoegh-Madsen S, Dam E, Henriksen K, Sondergaard BC, Pastoureau P, *et al.* Which elements are involved in reversible and irreversible cartilage degradation in osteoarthritis? Rheumatol Int 2010;30:435–42.
12. Findlay DM, Kuliwaba JS. Bone-cartilage crosstalk: a conversation for understanding osteoarthritis. Bone Res 2016;4:16028.
13. Felson DT, Neogi T. Osteoarthritis: is it a disease of cartilage or of bone? Arthritis Rheum 2004;50:341–4.
14. Brandt KD, Dieppe P, Radin EL. Etiopathogenesis of osteoarthritis. Rheum Dis Clin N Am 2008;34:531–59.
15. Watt I. Osteoarthritis revisited—again!. Skeletal Radiol 2009;38:419–23.
16. Lories RJ, Luyten FP. The bone-cartilage unit in osteoarthritis. Nat Rev Rheumatol 2011;7:43–9.
17. Johnston JD, Masri BA, Wilson DR. Computed tomography topographic mapping of subchondral density (CT-TOMASD) in osteoarthritic and normal knees: methodological development and preliminary findings. Osteoarthritis Cartilage 2009;17:1319–26.
18. Bousson V, Lowitz T, Laouisset L, Engelke K, Laredo J-D. CT imaging for the investigation of subchondral bone in knee osteoarthritis. Osteoporos Int 2012;23(Suppl 8):S861–5.
19. Omoumi P, Babel H, Jolles BM, Favre J. Quantitative Regional and Sub-regional Analysis of Femoral and Tibial Subchondral Bone Mineral Density (sBMD) Using Computed Tomography (CT): Comparison of Non-osteoarthritic (OA) and Severe Osteoarthritic Knees. Osteoarthritis Cartilage 2017;25(11):1850–7.
20. Radin EL, Rose RM. Role of subchondral bone in the initiation and progression of cartilage damage. Clin Orthop Relat Res 1986:34–40.
21. Burr DB, Gallant MA. Bone remodelling in osteoarthritis. Nat Rev Rheumatol 2012;8:665–73.
22. Eckstein F, Cicuttini F, Raynauld J-P, Waterton JC, Peterfy C. Magnetic resonance imaging (MRI) of articular cartilage in knee osteoarthritis (OA): morphological assessment. Osteoarthritis Cartilage 2006;14(Suppl A):A46–75.
23. Hunter DJ, Zhang W, Conaghan PG, Hirko K, Menashe L, Reichmann WM, *et al.* Responsiveness and reliability of MRI in knee osteoarthritis: a meta-analysis of published evidence. Osteoarthritis Cartilage 2011;19:589–605.
24. Stefanik JJ, Niu J, Gross KD, Roemer FW, Guermazi A, Felson DT. Using magnetic resonance imaging to determine the compartmental prevalence of knee joint structural damage. Osteoarthritis Cartilage 2013;21:695–9.
25. Guermazi A, Roemer FW, Felson DT, Brandt KD. Motion for debate: osteoarthritis clinical trials have not identified efficacious therapies because traditional imaging outcome measures are inadequate. Arthritis Rheum 2013;65:2748–58.
26. Buckwalter KA. CT arthrography. Clin Sports Med 2006;25:899–915.
27. Omoumi P, Mercier GA, Lecouvet F, Simoni P, Vande Berg BC. CT arthrography, MR arthrography, PET, and scintigraphy in osteoarthritis. Radiol Clin 2009;47:595–615.
28. Omoumi P, Rubini A, Dubuc J-E, Vande Berg BC, Lecouvet FE. Diagnostic performance of CT-arthrography and 1.5T MR-arthrography for the assessment of glenohumeral joint cartilage: a comparative study with arthroscopic correlation. Eur Radiol 2014;25:961–9.
29. Omoumi P, Michoux N, Larbi A, Lacoste L, Lecouvet FE, Perlepe V, *et al.* Multirater agreement for grading the femoral and tibial cartilage surface lesions at CT arthrography and analysis of causes of disagreement. Eur J Radiol 2017;88:95–101.
30. Edd SN, Omoumi P, Andriacchi TP, Jolles BM, Favre J. Modeling Knee Osteoarthritis Pathophysiology Using an Integrated Joint System (IJS): A Systematic Review of Relationships Among Cartilage Thickness, Gait Mechanics, and Subchondral Bone Mineral Density. Osteoarthritis Cartilage 2018;26(11):1425–37.
31. Cao Y, Stannus OP, Aitken D, Cicuttini F, Antony B, Jones G, *et al.* Cross-sectional and longitudinal associations between systemic, subchondral bone mineral density and knee cartilage thickness in older adults with or without radiographic osteoarthritis. Ann Rheum Dis 2014;73:2003–9.
32. Felson DT, McAlindon TE, Anderson JJ, Naimark A, Weissman BW, Aliabadi P, *et al.* Defining radiographic osteoarthritis for the whole knee. Osteoarthritis Cartilage 1997;5:241–50.
33. Omoumi P, Michoux N, Roemer FW, Thienpont E, Vande Berg BC. Cartilage thickness at the posterior medial femoral condyle is increased in femorotibial knee osteoarthritis: a cross-sectional CT arthrography study (Part 2). Osteoarthritis Cartilage 2014;23:224–31.
34. Moyer R, Wirth W, Duryea J, Eckstein F. Anatomical alignment, but not goniometry, predicts femorotibial cartilage loss as well as mechanical alignment: data from the Osteoarthritis Initiative. Osteoarthritis Cartilage 2016;24:254–61.
35. Kokkonen HT, Aula AS, Kroger H, Suomalainen J-S, Lammentausta E, Mervaala E, *et al.* Delayed computed tomography arthrography of human knee cartilage in vivo. Cartilage 2012;3:334–41.
36. Koo S, Gold GE, Andriacchi TP. Considerations in measuring cartilage thickness using MRI: factors influencing reproducibility and accuracy. Osteoarthritis Cartilage 2005;13:782–9.
37. Favre J, Erhart-Hledik JC, Blazek K, Fasel B, Gold GE, Andriacchi TP. Anatomically standardized maps reveal distinct patterns of cartilage thickness with increasing severity of medial compartment knee osteoarthritis. J Orthop Res 2017;35(11):2442–51.
38. Brown TD, Radin EL, Martin RB, Burr DB. Finite element studies of some juxtarticular stress changes due to localized subchondral stiffening. J Biomech 1984;17:11–24.
39. Johnston JD, Kontulainen SA, Masri BA, Wilson DR. A comparison of conventional maximum intensity projection with a new depth-specific topographic mapping technique in the CT analysis of proximal tibial subchondral bone density. Skeletal Radiol 2010;39:867–76.
40. Favre J, Scanlan SF, Erhart-Hledik JC, Blazek K, Andriacchi TP. Patterns of femoral cartilage thickness are different in asymptomatic and osteoarthritic knees and can be used to detect disease-related differences between samples. J Biomech Eng 2013;135:101002–10.
41. Wirth W, Eckstein F. A technique for regional analysis of femorotibial cartilage thickness based on quantitative magnetic resonance imaging. IEEE Trans Med Imag 2008;27:737–44.
42. Erhart-Hledik JC, Favre J, Andriacchi TP. New insight in the relationship between regional patterns of knee cartilage

thickness, osteoarthritis disease severity, and gait mechanics. J Biomech 2015;48:3868–75.
43. Frobell RB, Nevitt MC, Hudelmaier M, Wirth W, Wyman BT, Benichou O, *et al*. Femorotibial subchondral bone area and regional cartilage thickness: a cross-sectional description in healthy reference cases and various radiographic stages of osteoarthritis in 1,003 knees from the Osteoarthritis Initiative. Arthritis Care Res (Hoboken) 2010;62:1612–23.
44. Baum T, Sauerschnig M, Penzel J, Jungmann PM, Waldt S, Rummeny EJ, *et al*. Early changes of trabecular bone structure in asymptomatic subjects with knee malalignment. J Comput Assist Tomogr 2014;38:137–41.
45. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd edn. Routledge; 1998.
46. Chehab EF, Favre J, Erhart-Hledik JC, Andriacchi TP. Baseline knee adduction and flexion moments during walking are both associated with 5 year cartilage changes in patients with medial knee osteoarthritis. Osteoarthritis Cartilage 2014;22:1833–9.
47. Hart DJ, Cronin C, Daniels M, Worthy T, Doyle DV, Spector TD. The relationship of bone density and fracture to incident and progressive radiographic osteoarthritis of the knee: the Chingford Study. Arthritis Rheum 2002;46:92–9.
48. Hardcastle SA, Dieppe P, Gregson CL, Davey Smith G, Tobias JH. Osteoarthritis and bone mineral density: are strong bones bad for joints? Bonekey Rep 2015;4:624.
49. Prentice A, Parsons TJ, Cole TJ. Uncritical use of bone mineral density in absorptiometry may lead to size-related artifacts in the identification of bone mineral determinants. Am J Clin Nutr 1994;60:837–42.
50. Lo GH, Merchant MG, Driban JB, Duryea J, Price LL, Eaton CB, *et al*. Knee alignment is quantitatively related to periarticular bone morphometry and density, especially in patients with osteoarthritis. Arthritis Rheum 2018;70:212–21.