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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 OA knees

P. Omoumi † ‡ § *, H. Babel §, B.M. Jolles § ||, J. Favre §

† *Department of Diagnostic and Interventional Radiology, Centre Hospitalier Universitaire and University of Lausanne, Lausanne, Switzerland*
‡ *Department of Radiology, Cliniques Universitaires St Luc – UC Louvain, Brussels, Belgium*
§ *Swiss BioMotion Lab, Department of Musculoskeletal Medicine, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland*
|| *Institute of Microengineering, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland*

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SUMMARY

Objective: This study aimed to compare subchondral bone mineral density (sBMD) between non-radiographic osteoarthritic (OA) and medial femorotibial OA knees, using computed tomography (CT).
Design: CT exams from 16 non-radiographic OA (KL grade < 2) and 16 severe medial OA (KL grade ≥ 3) knees (average age of 61.7 ± 3 and 62.2 ± 5 years old respectively, 50% male in each group), were retrospectively analyzed. CT exams were segmented and 3D maps of sBMD based on the CT number in the most superficial 3 mm of femoral and tibial subchondral bone were computed. Average sBMD and medial-to-lateral sBMD ratios were calculated for total load-bearing regions and for sub-regions of interest in the femur and tibia.
Results: The analysis of total load-bearing regions did not reveal any significant difference between groups, except for the lateral tibia, where OA knees had lower sBMD. Sub-regional analysis unveiled differences with some sub-regions of the femur and tibia presenting significantly lower (in the lateral compartment) or higher (in the medial compartment) sBMD in OA knees compared to non-OA knees. The M/L sBMD ratios were significantly higher for OA knees compared to non-OA knees for all regions and sub-regions, except for the internal sub-regions.
Conclusions: sBMD locally differs between non-OA and OA knees, in agreement with prior knowledge on biomechanics. CT proved to be a valuable tool for 3D analysis of femoral and tibial sBMD, which can be used in future studies to describe the chronology of sBMD alterations and improve our understanding of the role of subchondral bone in knee OA.

Introduction

Although knee osteoarthritis (OA) has long been considered to be primarily a disease of cartilage, it is now considered as an organ-level failure of the joint, with recent research pointing to the role of other structural components, in particular the subchondral bone[1–3].

Since the description of Wolff's law in 1892, it is known that bone is influenced by the local mechanical environment[4]. The adaptive changes of bone to loading conditions could play a central role in the development of OA, particularly because loading alterations have been consistently reported with knee OA[5,6]. In particular, bone mineral density (BMD) changes in the subchondral bone (i.e., the region of bone located immediately underneath the cartilage that comprises the cortical plate and the subchondral cancellous bone) have been suggested as potential actors in the pathogenesis of cartilage degeneration[7].

However, to date, the mechanisms by which these changes in the subchondral bone may participate in the initiation or

* Address correspondence and reprint requests to: Patrick Omoumi, Department of Diagnostic and Interventional Radiology, Lausanne University Hospital, Bugnon 46, CH-1011 Lausanne, Switzerland. Tel.: 41-21-314-45-64; fax: 41-21-314-44-43.
E-mail address: pomoumi@gmail.com (P. Omoumi).

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progression of OA are still not fully understood[2,8]. It has been suggested that increased stiffness of subchondral bone reduces its ability to absorb and dissipate loads, hereby increasing mechanical constraints on the overlying cartilage and possibly contributing to cartilage degeneration[7]. While there is a number of studies regarding BMD and incidence and progression of knee OA, there is little data specifically on the subchondral BMD (sBMD)[3,9–11]. Additional research focusing on sBMD is required, particularly because the subchondral bone is where OA-related changes are most prominent[12]. In fact, it has been shown that the analysis of BMD closer to the articular surface is more prone to detect changes than analyses of BMD performed further away[13–16].

The lack of data on sBMD is mainly due to the limitations of the methods so far used to quantify BMD, particularly dual-energy X-ray absorptiometry (DXA), the most common modality. In fact, DXA is a two-dimensional technique with relatively low spatial resolution, which prohibits the assessment of local variations of BMD along the curved articular surfaces of the knee joint. Recently, computed tomography (CT) has been proposed as an alternative tool for the study of BMD at the knee[13,14,17,18]. This technique can provide quantitative data based on three-dimensional assessment, and the resolution of currently available CT scanners allows the analysis of specific regions such as the subchondral bone[17,18]. In fact, CT has already been shown to be a valid approach to map the sBMD of the tibia at high resolution, therefore offering a great opportunity to quantify sBMD with knee OA[13].

Prior research on cartilage morphology has reported local alterations with OA, suggesting that sBMD should also be analyzed for the total subchondral regions as well as using sub-regions of interest[19–22]. Translating such a sub-regional approach to the study of sBMD is now possible using the technical advantages of CT.

This study aimed to assess the sBMD of the femoral and tibial articular surfaces of the knee using CT, and to compare non-OA and medial femorotibial OA knees for total subchondral regions as well as for sub-regions of interest. Since the medial compartment has been shown to sustain more load than the lateral compartment in healthy knees and since this unbalance has been reported to increase with medial knee OA[23–25], and following the postulate that sBMD increases with higher loading, this study tested the hypotheses that:

1) sBMD is higher in the medial compartment than in the lateral compartment (i.e., medial-to-lateral sBMD ratio is greater than one) for both non-OA and OA knees, 2) sBMD is higher medially and lower laterally in OA compared to non-OA knees and medial-to-lateral sBMD ratios are higher in OA compared to non-OA knees, 3) sub-regional analysis is more sensitive at detecting OA-related differences than regional analysis.

Method

Population sample

In this case–control study, we retrospectively included two groups of non-OA ($n = 16$) and severe medial OA ($n = 16$) knees from 32 patients (one knee per patient). The sample size was determined based on the data published by Johnston *et al.* for tibial BMD, which indicated that groups of 16 knees were sufficient for the detection of statistically significant differences between non-OA and OA knees with a power of 0.8 and a type I error of 0.05.[13] All knees were randomly selected from the institution's database among patients above 50 years of age for whom CT arthrograms of the knees as well as lateral and postero-anterior weight-bearing radiographs were obtained on the same day. Any knees presenting imaging signs of the following conditions were excluded: previous bone fracture, previous knee surgery (including knee replacement procedures, ligamentoplasty, cartilage repair procedures) or poor image quality. Groups were assigned based on the grading of knee radiographs by a musculoskeletal radiologist with 7 years of experience, using a modified Kellgren–Lawrence (K/L) grade[26]. Each compartment was graded separately, leading to three separate 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, and a K/L grade <2 for the patello-femoral and lateral femorotibial compartments. Independent *t*-test indicated that there was no significant difference ($P > 0.7$) between groups for the age and bone morphometric parameters (biepicondylar femoral and the mediolateral tibial diameters, measured on axial CT images following previously published methodology[27]) (Table I). This study was approved by the institutional ethical committee (CEBHF: Comité d'éthique Biomédicale Hospitalo-Facultaire de l'UCL) without requirement for informed consent from participant due to the retrospective study design.

sBMD measurement

CT arthrograms

CT examinations were performed after intraarticular injection of 10 mL of ionic contrast material. Patients were positioned supine, with extension of the knee. Examinations were performed on a 40-detector row CT scanner (Somatom Definition AS; Siemens Healthcare, Forchheim, Germany): 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. CT examinations were acquired within 15 min after the injection, to avoid significant penetration of contrast media into surrounding tissues including cartilage and bone[28–30].

Post-processing of CT arthrograms

Regional and sub-regional sBMD quantifications were obtained in four steps, following previously published methods[13,31]. First, the tibial and femoral bones were segmented semi-manually on each CT arthrogram to build *3D surface models* of the bones with identification of the native subchondral areas (Fig. 1)[31]. The native subchondral areas were defined as bone areas covered by cartilage or underneath areas of full-thickness cartilage loss. We did not attempt to differentiate the subchondral bone plate from the underlying trabecular bone. Osteophytes were excluded from the segmentation. Second, *3D voxel models* were determined for each femur and tibia by identifying the CT voxels entirely contained inside the bone *surface models*. The voxels partially inside a bone *surface model* were not included in the *voxel models* to avoid border effects that could have affected the sBMD calculations in step four. The third step consisted in calculating 3D sBMD maps following the shape of the bones similar to maps presented in previous studies for cartilage thickness[32–34]. To this end, an sBMD value was calculated for each point of the subchondral areas of the bone *surface models* by averaging the CT intensity of the bone voxels within a distance of 3 mm to the point of interest (Fig. 1). The bone voxels within a distance of 3 mm were identified by intersecting the 3D bone *voxel models* with a sphere of 3 mm radius centered at the points of interest. The distance of 3 mm was selected based on prior literature to assess the BMD of the subchondral bone[13,34–36]. Finally, the forth step consisted in determining the average sBMD in standard regions and sub-regions of the subchondral tibial and femoral bones, using a subdivision that has been commonly used in the cartilage literature[21,37]. The tibia included two regions

Table I
Demographics of study participants

	Non-radiographic OA (MFT, LFT and PF K/L grades <2)	Severe MFT OA (MFT K/L grade ≥3 and LFT and FP K/L grades <2)	Comparison of Non-OA and OA groups (*P*-value)
Number (n)	16	16	
Gender (male)	50%	50%	
Age (year)	61.7 ± 2.8	62.2 ± 5.3	0.726*
Femur width (mm)	81.8 ± 8.0	81.5 ± 4.3	0.895*
Tibia width (mm)	74.1 ± 7.0	74.3 ± 5.0	0.929*
MFT KL grade = 0 (n)	11		
MFT KL grade = 1 (n)	5		
MFT KL grade = 3 (n)		11	
MFT KL grade = 4 (n)		5	

MFT: medial femorotibial compartment.
LFT: lateral femorotibial compartment.
PF: patellofemoral compartments.
* Student's *t*-test.

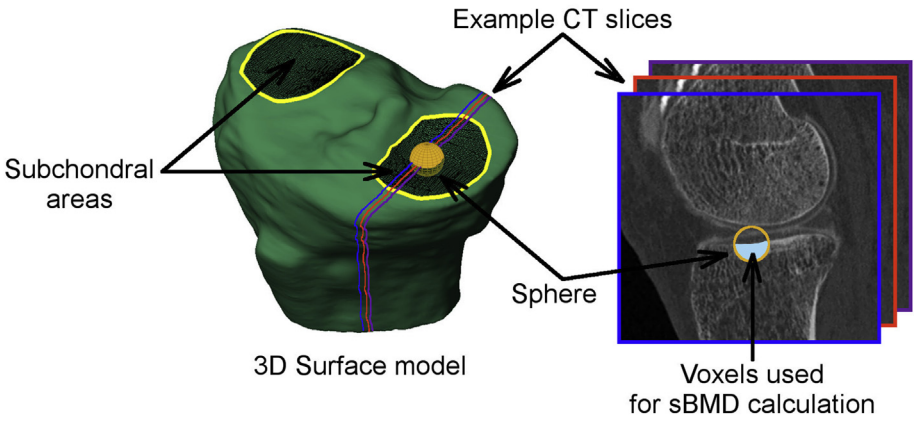

Fig. 1. Left: 3D surface model with identification of the native subchondral areas for a typical study tibia. Three example CT slices are delineated (blue, red and purple lines). The 3 mm diameter sphere used to calculate the local subchondral bone mineral density (sBMD) for a point of interest in the middle of the medial subchondral area is illustrated (orange sphere). Right: the same example CT slices as in the left part of the figure with illustration of the intersection between the sphere and the bone voxels. The local sBMD value was defined as the average value of the CT intensity of the voxels included both in the sphere and in the bone. Please note that this figure is an illustration and that proportions were altered to improve visibility.

corresponding to the total medial and lateral subchondral bone areas, respectively. These two regions were further split into five sub-regions (external, central, internal, anterior and posterior) (Fig. 2). Two regions corresponding to the load-bearing portions of the medial and lateral condyles were used for the femur. These two femoral regions were subsequently split into three sub-regions (external, central, internal). In addition, medial-to-lateral sBMD ratios were calculated by dividing the sBMD values in the medial and lateral compartments. All processing was done with custom software implemented using Matlab (R2014b, Mathworks, Natick, MA).

Statistical analysis

Since all sBMD variables were normally distributed (confirmed by one-sample Kolmogorov–Smirnov tests), the statistical analyses were performed using two-sided Student's *t*-tests. Specifically, one sample *t*-tests were performed to determine if the medial-to-lateral sBMD ratios were significantly different from 1. Additionally, independent two samples (unpaired) *t*-tests were performed to compare sBMD values between the non-OA and OA groups. Each hypothesis was tested using one or two groups of 16 observations. All observations were independent (independent knees in each group and independent regions and sub-regions). All statistical analyses were performed using Matlab (2014b, MathWorks, Natick, MA) and an alpha-level set a priori at 5% was considered for all tests. Significance refers to statistical significance unless specified otherwise.

Results

Comparison of sBMD between medial and lateral compartments (Fig. 2, dash symbols in Tables II and III)

In both non-OA and OA knees, the medial compartment showed significantly higher sBMD than the lateral compartment for both the total load-bearing regions (M/L ratios > 1, $P < 0.001$), and the sub-regions (M/L ratios > 1, $P < 0.01$), except for the external femoral ($P = 0.919$) and posterior tibial ($P = 0.670$) sub-regions in non-OA knees (Fig. 2, dash symbols in Tables II and III).

Comparison of sBMD between OA and non-OA knees (Fig. 3, star symbols in Tables II and III)

When comparing the total load-bearing regions, sBMD was not significantly different between OA and non-OA knees ($P > 0.162$), except for the lateral tibial region, which presented significantly lower sBMD in OA compared to non-OA knees ($P = 0.03$) (Fig. 3(a), Tables II and III).

The sub-regional analysis confirmed the lower sBMD for OA knees in some sub-regions of the lateral tibia (Fig. 3(b), Table III). The sub-regional analysis additionally detected higher sBMD in the

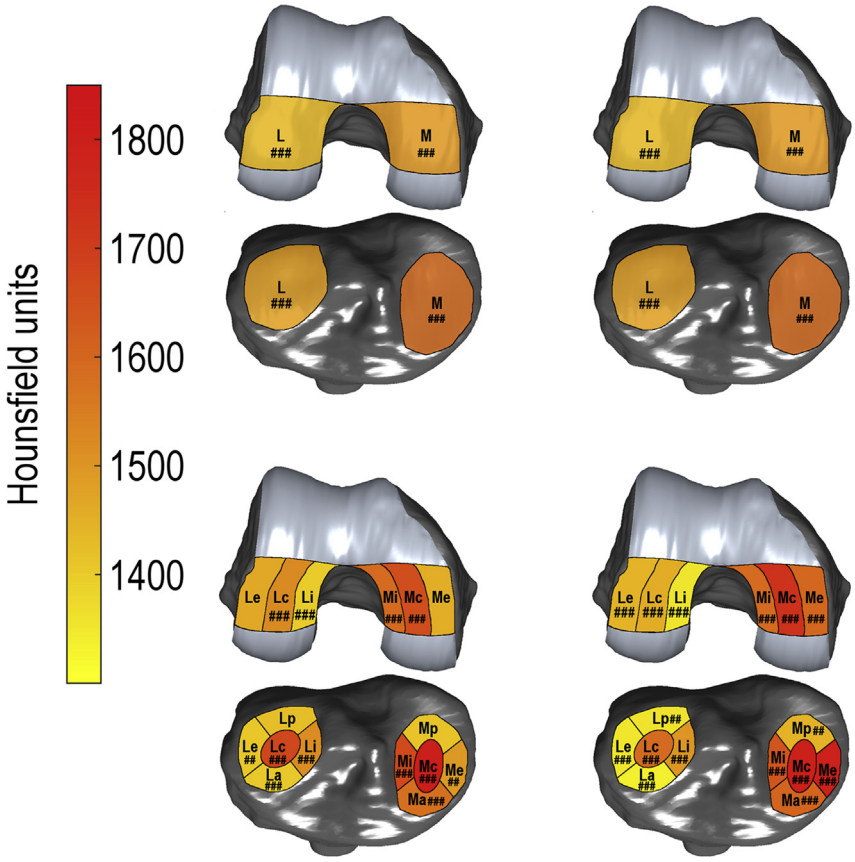

Fig. 2. sBMD in femorotibial load-bearing regions (upper two rows), and subregions (lower two rows) in non-OA (left column) and OA knees (right column). The dashed symbols indicate areas for which medial-to-lateral ratios significantly different from 1 ($^{\#}$: $P < 0.05$, $^{\#\#}$: $P < 0.01$, $^{\#\#\#}$: $P < 0.001$).

medial femoral and tibial compartments, as well as lower sBMD in the lateral femur (Fig. 3(b), Tables II and III). Specifically, regarding the femoral sub-regions, the sBMD was significantly higher for OA compared to non-OA knees in the medial external ($P = 0.006$) and central ($P = 0.04$) sub-regions, and significantly lower in the lateral central sub-region ($P = 0.029$). Regarding the tibial sub-regions, the sBMD was significantly higher for OA compared to non-OA knees in the medial external sub-region ($P < 0.001$), and significantly lower in the lateral central ($P \leq 0.039$) and anterior ($P = 0.002$) sub-regions. All other tibial and femoral sub-regions did not significantly differ between OA and non-OA knees ($P > 0.052$).

The M/L sBMD ratios were significantly higher for OA knees compared to non-OA knees in both the femoral ($P = 0.008$) and tibial ($P < 0.001$) total load-bearing regions (Fig. 3(a), Tables II and III). These results agreed with the sub-regional analysis, as the M/L sBMD ratios were also significantly higher for OA compared to non-OA knees in all femoral ($P < 0.002$) and tibial ($P < 0.03$) sub-regions, except for the internal femoral ($P = 0.076$) and tibial ($P = 0.911$) sub-regions (Fig. 3(b), Tables II and III).

Table II
Femoral subchondral bone mineral density (sBMD)

	Non-radiographic OA ($n = 16$)	Severe MFT OA ($n = 16$)
Medial compartment		
Total (M)	1532.6 ± 80.0	1570.7 ± 70.2
External (Me)**	1456.8 ± 91.3	1597.8 ± 166.3
Central (Mc)*	1654.5 ± 89.0	1730.8 ± 111.3
Internal (Mi)	1588.1 ± 71.3	1591.9 ± 100.1
Lateral compartment		
Total (L)	1462.4 ± 76.0	1429.3 ± 67.4
External (Le)	1463.8 ± 67.4	1444.3 ± 70.7
Central (Lc)*	1525.4 ± 87.6	1457.6 ± 78.8
Internal (Li)	1401.0 ± 91.1	1354.3 ± 86.3
Medial-to-lateral ratio		
Total (M/L)**	1.05 ± 0.05$^{\#\#\#}$	1.10 ± 0.05$^{\#\#\#}$
External (Me/Le)**	1.00 ± 0.08	1.11 ± 0.10$^{\#\#\#}$
Central (Mc/Lc)***	1.09 ± 0.05$^{\#\#\#}$	1.19 ± 0.08$^{\#\#\#}$
Internal (Mi/Li)	1.13 ± 0.03$^{\#\#\#}$	1.18 ± 0.09$^{\#\#\#}$

Data are sBMD in Hounsfield units, presented as mean ± standard deviation over a group of 16 non-OA or OA knees.
The dash symbols indicate medial-to-lateral ratios significantly different from 1 (one sample Student's *t*-test) ($^{\#}$: $P < 0.05$, $^{\#\#}$: $P < 0.01$, $^{\#\#\#}$: $P < 0.001$).
The star symbols indicate significant differences between non-OA and OA groups (Student's *t*-test for independent samples) (*: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$).

Discussion

Our results bring support to the three study hypotheses. First, the sBMD was significantly higher in the medial compared to the lateral compartment in all regions and in almost all sub-regions for both the non-OA and OA groups (as shown by medial-to-lateral ratios greater than 1). These findings are consistent with previous results from DXA imaging and peripheral quantitative CT (pQCT), and can be explained by the fact that the medial compartment sustains higher loads than the lateral compartment in both non-OA and medial OA knees[14,15,23–25,38]. While differences in BMD between medial and lateral tibias have been described in the literature for quite some time, it is only the recent emergence of CT-based analysis of sBMD that allowed the present study to test and quantify them for the femur as well.

Table III
Tibial sBMD

	Non-radiographic OA ($n = 16$)	Severe MFT OA ($n = 16$)
Medial compartment		
Total (M)	1623.5 ± 101.7	1661.9 ± 70.2
External (Me)***	1493.6 ± 132.6	1790.5 ± 170.1
Central (Mc)	1804.3 ± 133.6	1793.4 ± 83.2
Internal (Mi)	1667.9 ± 131.5	1642.0 ± 135.4
Anterior (Ma)	1578.0 ± 104.6	1600.6 ± 121.8
Posterior (Mp)	1415.1 ± 75.0	1445.8 ± 109.7
Lateral compartment		
Total (L)*	1512.9 ± 77.3	1449.2 ± 80.4
External (Le)	1408.0 ± 82.8	1352.8 ± 70.9
Central (Lc)*	1674.7 ± 110.9	1591.9 ± 106.0
Internal (Li)	1518.4 ± 94.8	1501.4 ± 103.7
Anterior (La)**	1406.4 ± 55.5	1337.2 ± 59.9
Posterior (Lp)	1425.9 ± 79.9	1361.8 ± 111.0
Medial-to-lateral ratio		
Total (M/L)***	1.07 ± 0.05###	1.15 ± 0.05###
External (Me/Le)***	1.06 ± 0.08##	1.33 ± 0.17###
Central (Mc/Lc)*	1.08 ± 0.05###	1.13 ± 0.07###
Internal (Mi/Li)	1.10 ± 0.09###	1.10 ± 0.10###
Anterior (Ma/La)**	1.12 ± 0.06###	1.20 ± 0.07###
Posterior (Mp/Lp)**	0.99 ± 0.06	1.07 ± 0.08##

Data are sBMD in Hounsfield units, presented as mean ± standard deviation over a group of 16 non-OA or OA knees.
The dash symbols indicate medial-to-lateral ratios significantly different from 1 (one sample Student's *t*-test) (#: $P < 0.05$, ##: $P < 0.01$, ###: $P < 0.001$).
The star symbols indicate significant differences between non-OA and OA groups (Student's *t*-test for independent samples) (*: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$).

Second, as hypothesized, the medial-to-lateral sBMD ratios were significantly higher in knees with medial femorotibial OA compared to non-OA knees for all regions and sub-regions, except the internal sub-regions of the femur and tibia. Higher sBMD medially and lower sBMD laterally were also consistently observed in several sub-regions of OA knees. These results might be explained by the biomechanical changes occurring with medial femorotibial OA, usually associating a varus deformity and lateral translation of the tibia[39–41]. These biomechanical differences lead to increased stress on the most external aspect of the medial compartment, while the most internal aspects of the same compartment are spared. The biomechanical differences also result in decreased stress on the lateral compartment, altogether increasing the medial-to-lateral loading ratios[24,42]. Prior reports using DXA imaging and pQCT have found conflicting results as to the changes in BMD occurring with OA[3,14,43]. These inconsistencies might be due to the fact that previous studies, opposite to ours, were technically limited to the analysis of trabecular bone located further away from the surface, where the influence of mechanical stress is less than in the subchondral bone[14–16].

Third, sub-regional comparisons of sBMD detected more differences between the non-OA and OA groups than the analysis of the total load-bearing regions. This higher sensitivity could be explained by the spatial variations in sBMD alterations occurring with OA. In fact, it is possible that OA is associated with consistent differences (higher or lower sBMD) in one location and inconsistent sBMD differences in other locations, all within a same load-bearing region. Therefore, considering the average difference over the total load-bearing region could mask the local difference that does exist. Similar observations were already reported for cartilage thickness, where sub-regional analyses detected more differences with OA severity[19,20,44]. In addition to improving the sensitivity of detecting OA-related differences, sub-regional analyses also provide information regarding the location of sBMD differences, which could prove important to improving our understanding of knee OA pathophysiology and assessing the efficiency of therapeutic interventions (e.g., by indicating where bone structure and biology should be tested).

The present study has several strengths compared to previous reports on BMD and OA, specifically in terms of the spatial resolution provided by CT relative to DXA imaging and pQCT. In fact, the CT-based method in this study allowed the assessment of the subchondral bone immediately located under the surface of cartilage, following the contours of the articular surfaces of both the femur and tibia. This allowed us to analyze sub-regions of both the flat surface of the tibia as well as the curved femoral condyles and account for spatial variations under the entire articular surfaces of the femorotibial joint, which is impossible to perform using previous methods (and which, to the best of our knowledge, has never been performed so far). The high-resolution 3D capability of CT represents a significant strength, as each area of the articulating femorotibial joint

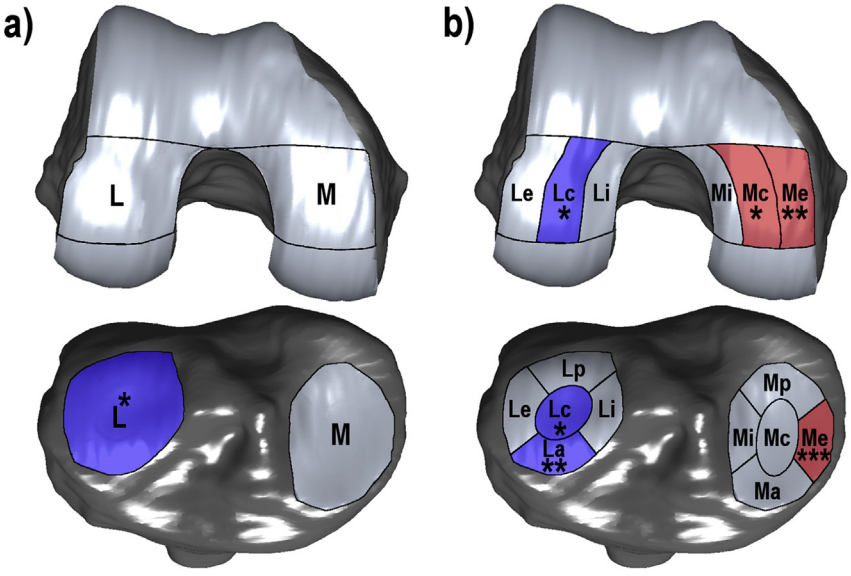

Fig. 3. Comparison of sBMD in femorotibial load-bearing regions (a) and sub-regions (b) between severe femorotibial OA and non-radiographic OA knees. Significant differences are color-coded: red = significantly higher values for OA; blue = significantly lower values for OA (*: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.001$).

surface presents different functions that may translate in spatial sBMD variations[8,15]. We showed that this 3D capability could be valuable to detect sub-regional sBMD differences with knee OA. It is also worth noting that the present study used standard sub-regions previously developed for the analyses of cartilage morphology, hereby allowing comparisons to previous research in this field[21,37].

This study also presents several limitations, including the cross-sectional design and the fact that only severe medial OA knees were tested. While further studies with larger populations at various stages of the disease will be necessary to better understand sBMD alterations with knee OA, the present results already achieved a first step by showing the potential of CT as a tool to analyze sub-regional alterations of sBMD related to OA in both the femur and the tibia. Another limitation was the fact that although we did attempt to account for biases such as differences in bone size between groups, our retrospective design did not allow us to account for other variables such as, height, weight or Bone Mass Index that could influence sBMD. Moreover, CT is intrinsically limited to the assessment of apparent BMD (as opposed to true mineral density): the non-mineral components of bone tissue (such as fat, blood vessels, resorption cavities) contained in each voxel are taken into account when measuring the attenuation of that voxel[17]. In theory, these components can represent a bias in the measurements. However, in the first 3 mm of subchondral bone, the mineral components largely predominate and the influence of non-mineral components of bone is likely negligible. Another technical limitation includes the use of a bone kernel, which might lead to ringing artifacts at the interfaces. However, by measuring the sBMD in the most superficial 3 mm of the subchondral bone, the effects of this potential artifact are most likely negligible. Finally, due to limited sample size, we could not analyze the data for male and females separately.

Finally, it is to note that we used HU, a standardized CT attenuation coefficient, as a surrogate to BMD. CT attenuation coefficients can vary between exams depending on several factors such as scanner model, acquisition parameters and patient habitus[45]. To allow calibration of these parameters between scans, phantoms can be scanned with the patient for each examination[46]. Phantom-less BMD measurement techniques are even available on new generation scanners, with some allowing calibration at a different time from the patient scan[47–50]. Since the knees in this study were scanned without a phantom and since current phantom-less methods are not adapted to the presence of intra-articular iodine, we quantified sBMD using HU. However, in order to optimize the homogeneity of the acquisition parameters to avoid any bias related to the variability of CT numbers, all examinations were performed on the same scanner, using the same acquisition parameters, including automatic dose modulation protocols. Therefore, the absence of calibration to mg/cm^3 should have little effect on the differences observed between non-OA and OA groups, but limits comparisons with other studies from other groups.

In conclusion, this study pointed to the value of CT in analyzing sBMD in the knee and reported meaningful differences between non-OA and severe medial OA knees. Questions still remain in order to further elucidate the role of subchondral bone in the pathogenesis and progression of OA. Specifically, there is a need to determine the patterns and chronology at which these changes occur. CT provides a quantitative tool for a sub-regional 3D analysis of sBMD of both the femur and tibia that could be used in longitudinal studies to fill the knowledge gaps on the role of subchondral bone in OA, which is a prerequisite to improve the diagnosis and treatment of this condition.

Contributions

PO and JF 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.

BMJ 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.

HB 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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