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BMI-Related Microstructural Changes in the Tibial Subchondral Trabecular Bone of Patients With Knee Osteoarthritis

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ABSTRACT: Overweight is a risk factor for osteoarthritis on the knees. Subchondral trabecular bone (SCTB) densification has been shown to be associated with cartilage degeneration. This study analyzed the microarchitectural changes in the SCTB of tibial plateaus to validate the hypothesis that the degree of remodeling is correlated with a patient's body weight. Twenty-one tibial plateaus were collected during total knee arthroplasty from 21 patients (15 women and 6 men). These patients had a mean age of 70.4 years (49–81), mean weight of 74.7 kg (57–93) and mean body mass index (BMI) of 28.4 kg/m^2 (21.3–40.8). One cylindrical plug was harvested in the center of each tibial plateau (medial and lateral). Micro-CT parameters (7.4 μm resolution) were determined to describe the SCTB structure. On the medial plateau, there were significant correlations between BMI and bone volume fraction BV/TV ($r = 0.595$, $p = 0.004$), structure model index SMI ($r = -0.704$ $p = 0.0002$), trabecular space Tb.Sp ($r = 0.600$, $p = 0.04$) and trabecular number Tb.N ($r = 0.549$, $p = 0.01$). SCTB densification during osteoarthritis is associated with a reduction in its elastic modulus, which could increase cartilage stress, and accelerate cartilage loss. SCTB densification has been shown to precede cartilage degeneration. The correlation of SCTB microarchitecture and body weight may explain why knee osteoarthritis is more common in overweight or obese patients.

Keywords: osteoarthritis; obesity; weight; subchondral bone; microstructure

Osteoarthritis of the knee can lead to severe functional disability. The risk of knee osteoarthritis increases greatly with age: the prevalence is 5% at age 55 but increases to 40–50% in those over 80 years of age.[1] Many factors beyond age and physiological aging of the joint have been identified to explain the complex, multifactorial pathophysiology of knee osteoarthritis.[2] A patient's body weight is one of the main predisposing factors. This has been confirmed by the statistical relationship between excess weight and early, rapid development of knee osteoarthritis.[1,3]

Being overweighted ($BMI > 25$)[4] places excessive mechanical loads on a person's knees[5] and contributes to degenerative arthritis of the knee. The pathophysiology of this phenomenon is not well defined. Densification of subchondral trabecular bone (SCTB) is a classic radiographic sign of osteoarthritis, no matter which joint is affected. It is very clearly visible at the proximal tibial on standard radiographs in knee osteoarthritis patients. In terms of micro-architecture, this translates to changes in microstructural parameters that can be analyzed by micro-computed tomography (micro-CT): increase in the bone volume fraction (BV/TV), increase in trabecular thickness (Tb.Th) and reduction in the structure model index (SMI).[6–8]

In parallel, studies have demonstrated that a chronological relationship[9] or association[10] exists between changes in these microarchitectural parameters and the development of osteoarthritis in animal models. Thickening of subchondral bone and increases in Tb.Th and BV/TV precede chondrocyte apoptosis and cartilage degeneration. Subchondral bone remodeling may be a factor leading to chondrocyte apoptosis.[9] Microarchitectural remodeling of subchondral bone may be the link between excess weight and knee osteoarthritis.

We hypothesized that in knee osteoarthritis, the magnitude of SCTB microarchitectural changes and remodeling in the tibial plateaus are correlated with a patient's weight. The primary objective of this study was to determine if a correlation exists between tibial plateau SCTB microstructural changes and body weight. The secondary objective was to verify the correlation between microarchitectural parameters and other patient patterns.

MATERIALS AND METHODS

Patient Selection

After gaining approval from our institutional review board and obtaining informed consent from our patients, 21 tibial plateaus were collected during total knee arthroplasty (TKA) from 21 patients who had been diagnosed with primary knee osteoarthritis based on clinical and radiographic criteria. Any medical and surgical histories were noted. Patients were excluded if the TKA indication was something other than primary osteoarthritis (e.g., rheumatoid arthritis, osteonecrosis, posttraumatic osteoarthritis), there was a history of tibial and/or femoral osteotomy or of long-term corticosteroid therapy or bisphosphonate treatment. The patient's weight and height were recorded preoperatively and the BMI calculated, making

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Table 1. Clinical and Radiographic Preoperative Data

Case Number	Age (Years)	Weight (kg)	Height (m)	BMI (kg/m^2)	Sex	Side	OA Medial/Lateral	Comorbidities
1	49	72	1.75	23.5	M	Right	Medial	Neither T2DM or HT
2	69	90	1.72	30.4	M	Right	Medial	T2DM and HT
3	67	67	1.60	26.2	F	Right	Medial	Neither T2DM or HT
4	62	93	1.51	40.8	F	Left	Medial	HT
5	66	75	1.69	26.3	F	Left	Medial	HT
6	79	72	1.78	22.7	M	Right	Lateral	HT
7	79	63	1.50	28.0	F	Left	Lateral	HT
8	68	73	1.67	26.2	F	Right	Lateral	HT
9	65	68	1.55	28.3	F	Left	Lateral	Neither T2DM or HT
10	80	86	1.56	35.3	F	Left	Medial	HT
11	80	86	1.74	28.4	F	Left	Medial	Neither T2DM or HT
12	73	70	1.58	28.0	F	Left	Medial	T2DM
13	65	92	1.64	34.2	M	Left	Lateral	T2DM and HT
14	70	63	1.55	26.2	F	Left	Medial	Neither T2DM or HT
15	79	63	1.72	21.3	M	Right	Medial	Neither T2DM or HT
16	81	57	1.58	22.8	F	Right	Lateral	HT
17	50	80	1.84	23.6	M	Left	Medial	Neither T2DM or HT
18	75	78	1.59	30.9	F	Right	Medial	Neither T2DM or HT
19	68	90	1.59	35.6	F	Left	Medial	Neither T2DM or HT
20	80	65	1.60	25.4	F	Right	Lateral	HT
21	74	65	1.55	27.1	F	Right	Medial	T2DM

HT, hypertension; OA, osteoarthritis; T2DM, type 2 diabetes mellitus.

sure that the patient's weight had not changed during the year leading up to the surgery. Patients underwent a preoperative radiographic assessment consisting of standard A/P and lateral radiographs, and schuss view of the knee (A/P view with patient standing on single leg in 30° flexion) to confirm the presence of osteoarthritis and its stage. There were 15 women and 6 men. The mean age at the time of surgery was 70.4 ± 9 years (49–81). Eleven patients were less than 70 years old (young subgroup) and 10 were more than 70 years old (old subgroup). The mean weight was 74.7 ± 10.8 kg (57–93) and the mean height was 163 ± 9 cm (150–184). The mean BMI was $28.1 \pm 4.8\ kg/m^2$ (21.3–40.8); five patients had a normal weight ($BMI \leq 25$), 11 patients were overweight ($25 < BMI \leq 30$) and five were obese ($BMI > 30$).

Specimen Preparation

The tibial plateaus were harvested during knee surgery cutting perpendicular to tibia axis on the proximal epiphysis. Samples were frozen for storage at −18°C. One cylindrical plug was harvested by drilling the frozen bone in the center of the medial and lateral parts of each tibial plateau. Each specimen was 10 mm in diameter to ensure that sufficient bone tissue was available to obtain reliable numerical data and avoid cutting-related artifacts. The region of interest was the central weight-bearing portion. The orientation of the cylindrical plug was carefully checked to ensure that the longitudinal axis of the tibia corresponded to that of the cylindrical specimen.

Microstructural Analysis

A micro-CT system (Skyscan® 1174, Bruker micro-CT, Kontich, Belgium) was used to determine the microarchitecture of the tibial plateau's SCTB. Each specimen was placed in a cylindrical sample holder in Ringer's solution to prevent movement and changes in the micro-CT parameters due to drying during the scanning process. Each plug was scanned continuously in 7.4 μm thick slices. The voxel size was $7.4 \times 7.4 \times 7.4$ μm. Boundaries and cartilage zones were carefully excluded to avoid artifacts. The regions of interest (ROI, 8,5 mm in diameter and 5 mm in height) were located in the center of the SCTB of the specimen under the tibial plateau's subchondral plate, which was excluded from the analysis. The same procedure was used to select all the ROIs in all plugs. The following three-dimensional parameters were used to describe the SCTB structure: bone volume fraction (BV/TV); specific bone surface (BS/BV); trabecular number (Tb.N); trabecular thickness (Tb.Th); trabecular separation (Tb.Sp); trabecular pattern factor (Tb.Pf); degree of architectural anisotropy (DA), and structure model index (SMI).

Statistical Analysis

Calculations were performed with Statview® software (SAS Institute Inc., Cary, NC). Nominal variables were reported as sample sizes and percentages. Continuous variables were described by the mean, standard deviation, maximum and minimum. Normal data distribution was verified. The groups were compared with an independent Student's t-test if the data were normally distributed and a nonparametric test if they were not. A Chi-square test was performed on nominal variables if the expected frequencies were five or more; if not, a Fischer's exact test was carried out. Correlations r were determined using Pearson or Spearman correlation or determination coefficients r^2 with 95% confidence intervals. The significance threshold was set at $p < 0.05$.

RESULTS

The radiographs identified 14 cases of predominantly medial osteoarthritis with varus deformity and seven

Table 2. Micro-CT Data

Case Number	BV/TV		BS/BV		SMI		Tb.Th (μm)		Tb.N (1/mm)		Tb.Sp (μm)		Tb.Pf	
	Medial	Lateral	Medial	Lateral	Medial	Lateral	Medial	Lateral	Medial	Lateral	Medial	Lateral	Medial	Lateral
Mean ± SD (min; max)	34.82 ± 10.81 (17.45; 58.97)	26.94 ± 8.85 (14.11; 43.81)	18.70 ± 3.58 (13.04; 27.09)	19.81 ± 3.88 (13.71; 31.84)	-0.33 ± 1.67 (−3.5; 2.1)	0.61 ± 1.25 (−1.60; 2.78)	228 ± 42 (128; 332)	207 ± 36 (151; 297)	1.64 ± 0.29 (1.17; 2.11)	1.41 ± 0.27 (0.86; 1.81)	456 ± 89 (283; 631)	509 ± 82 (393; 693)	−6.173 ± 6.596 (−25.492; 2.780)	−1.548 ± 5.030 (−16.033; 4.083)

BV/TV, bone volume fraction; BS/BV, specific bone surface; SMI, structure model index; Tb.Th, trabecular thickness; Tb.N, trabecular number; Tb.Sp, trabecular separation; Tb.Pf, trabecular pattern factor.

cases of predominantly lateral osteoarthritis with valgus deformity. The entire set of preoperative clinical and radiological data is presented in Table 1.

The results of the micro-CT analysis of the medial and lateral plateaus are given in Table 2 (BV/TV, BS/BV, SMI, Tb.Th, Tb.N, Tb.Sp, Tb.Pf). There was no significant gender difference in the mean values ($p > 0.05$) for any of the microarchitectural data, either medially and laterally; therefore, the data were pooled for the remaining analyses.

Weight and BMI were significantly correlated to microarchitectural parameters in the medial plateau (BV/TV, SMI, Tb.Th, Tb.N) (Table 3). There were strong correlations between BMI and BV/TV ($r = 0.595$, $p = 0.004$), SMI ($r = -0.704$ $p = 0.0002$), Tb. Sp ($r = 0.600$, $p = 0.04$) and Tb.N ($r = 0.549$, $p = 0.01$) (Fig. 1A, B, and C; Fig. 2A and B). Some of the microarchitectural parameters in the medial tibial plateau varied based on patient weight (Table 4 and Fig. 3A and B). However, none of the endostructure pattern was significantly correlated with the patient's height. None of the parameters measured in the lateral plateau samples were correlated with height, weight or BMI.

Porosity tended to increase with age ($r = 0.558$, $p = 0.016$) in the medial tibial plateaus. This was associated with a significant decrease in Tb.N ($r = -0.384$, $p = 0.08$) (Fig. 4A and B; Fig. 5A and B). In the subgroup of patients under 70 years of age, the bone network was denser (BV/TV = 42.4 ± 9% vs. 34.8 ± 9.8%, $p = 0.23$), contained more trabeculae (Tb.N = 1.88 ± 0.36 vs. 1.72 ± 0.18, $p = 0.054$) than in patients above 70 years of age.

DISCUSSION

To our knowledge, this is the first study showing a significant correlation between changes in various microarchitectural parameters and the weight of patients with knee osteoarthritis. These correlations are even stronger when BMI is taken into account. Wen et al.[11] evaluated the effect of type 2 diabetes mellitus (T2DM) and hypertension on bone mineral density (BMD) of the subchondral plate and SCTB porosity in the medial plateau of arthritic knees. In their study, 79% of patients were overweight or obese, 63% suffered from hypertension and 30% had T2DM. Hypertension and T2DM were associated with a significant reduction in the subchondral plate BMD and an increase in the SCTB porosity. They also found a significant decrease in subchondral plate BMD and an increase in SCTB porosity as BMI increased. These results differ from those in the current study. We found an increase in the bone volume fraction (BV/TV) and trabecular thickness and intertrabecular connectivity as BMI increased. Our study showed a direct relationship between remodeling of the tibial plateaus in arthritic knees and body weight; excess weight places additional demands on the bone to which it must adapt mechanically. The limits of our study were

Table 3. Correlations Between Micro-CT Parameters and Weight, Height, BMI, and Age

	Weight	Height	BMI	Age
BV/TV medial	0.504 [0.163:0.796], $p = 0.02$	−0.219 [−0.605:0.220], $p = 0.34$	0.595 [0.310:0.847], $p = 0.004$	−0.295 [−0.701:0.055], $p = 0.194$
BS/BV medial	−0.216 [−0.752: −0.054], $p = 0.347$	0.225 [−0.093:0.681], $p = 0.326$	−0.318 [−0.828: −0.252], $p = 0.160$	0.131 [−0.281:0.562], $p = 0.57$
SMI medial	−0.340 [−0.765: −0.083], $p = 0.03$	0.342 [−0.043:0.707], $p = 0.129$	−0.704 [−0.871: −0.392], $p = 0.0002$	0.217 [−0.237:0.593], $p = 0.36$
Tb.Th medial	0.042 [−0.241:0.708], $p = 0.858$	−0.218 [−0.736: −0.017], $p = 0.342$	0.179 [0.275:0.836], $p = 0.436$	−0.063 [−0.505:0.352], $p = 0.786$
Tb.N medial	0.530 [−0.029:0.714], $p = 0.014$	0.618 [−0.294:0.552], $p = 0.116$	0.549 [−0.170:0.636], $p = 0.010$	−0.384 [−0.780: −0.121], $p = 0.085$
Tb.Sp medial	−0.440 [−0.664:0.124], $p = 0.046$	−0.296 [−0.564:0.278], $p = 0.192$	−0.600 [−0.580:0.256], $p = 0.04$	0.187 [0.096:0.770], $p = 0.416$
Porosity	−0.168. $p = 0.505$	−0.001. $p = 0.996$	−0.170. $p = 0.501$	0.558. $p = 0.016$

Correlations are expressed using Pearson or Spearman correlation coefficients (r [CI 95%]. p-value).

the absence of non-arthritic young or old people as witness and the little numbers of cases but our results confirm our hypothesis that a patient's weight and BMI affect the SCTB microstructure (Table 3).

While an increase in body weight is associated mainly with an increase in trabecular thickness (Tb.Th), intertrabecular connectivity (Tb.Pf) and bone volume fraction (BV/TV) in arthritic knees, the number of trabeculae decreases (Tb.N) and trabecular separation (Tb.Sp) increases, resulting in significantly lower bone bone volume fraction (BV/TV) with age. The correlation between age and these microarchitectural data has already been demonstrated.[12–14] In healthy knees, these age-

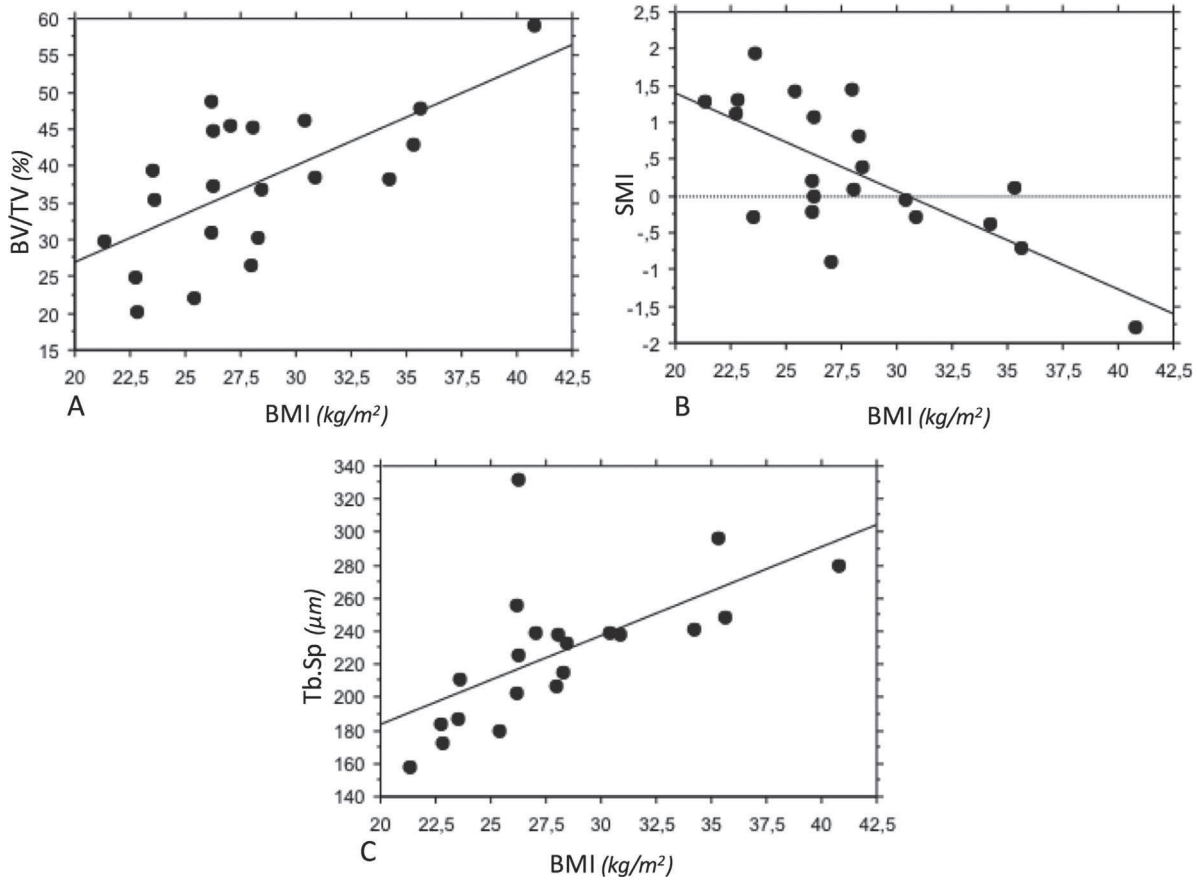


Figure 1. Correlation of body mass index (kg/m^2) with bone volume fraction (BV/TV) $r = 0.595$, $p = 0.004$ (A), structure model index (SMI) $r = -0.704$ $p = 0.0002$ (B) and trabecular space (Tb.Sp) $r = 0.600$, $p = 0.04$ (C) for the medial tibial plateau.

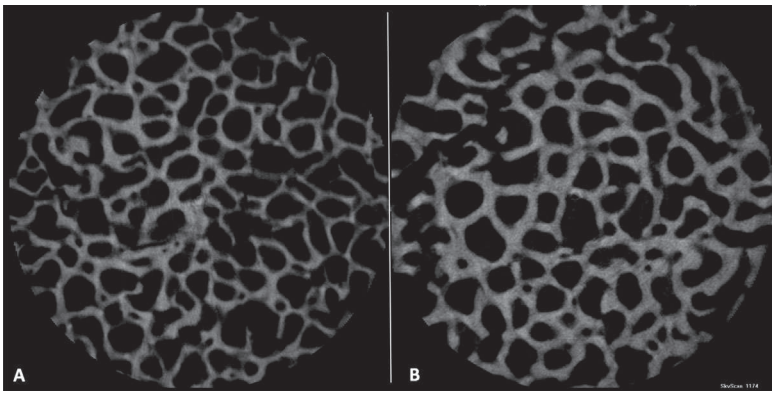


Figure 2. Micro-CT slices showing the effect of weight and BMI on the architecture of subchondral trabecular bone of the medial tibial plateau: (A) case 1, 49-year-old man with BMI of 23.5 (BV/TV = 27.88) and (B) case 19, 68-year-old woman with BMI of 35.6 (BV/TV = 38.77).

related changes affect both tibial plateaus in a similar manner.[13] Ding et al.[14] found a reduction in trabecular thickness (Tb.Th) and an increase in the SMI (to a more rod-like structure) especially after 60 years of age. They reported no significant decrease in the number of trabeculae (Tb.N). This was associated with a significant decrease in the SCTB mechanical properties in these subjects with a reduction in stiffness and Young's modulus.[15] Chen et al.[16] had similar findings in an Asian population but also found this decrease to be lesser in men than women. In the current study, these differences were found only in the medial tibial plateaus, while Ding et al.[12] had found this in both the medial and lateral condyles. In early osteoarthritis, these changes are mainly found in the most damaged compartment.[6]

We hypothesized that in knee osteoarthritis, the magnitude of SCTB microarchitectural changes and remodeling in the tibial plateaus are correlated to patient weight. This could explain the high prevalence of knee osteoarthritis in overweight and obese patients. This led us to analyze the SCTB microarchitectural parameters in the tibial plateaus of arthritic knees based on weight and BMI. The values were similar and consistent with those found by other groups for arthritic tibial plateaus.[6–8,18] The small differences between this and certain other studies can be attributed to the higher voxel size used in the current study (7.4 μm) versus 15 μm for Chen et al.[16] 22 μm for Ding et al.[6] 26 μm for Patel al.[18] or 22 μm for Ding[14]. The micro-CT system used in the current study has similar reliability to other systems.[19]

Table 4. Micro-CT Data by Weight Subgroup

BMI Subgroups		Mean	SD	IC 95		*F*	*p*
BV/TV	BMI_under25	26.16	2.89	18.12	34.19		
	BMI_25to30	35.42	3.04	28.54	42.30	3.184	0.065
	BMI_over30	41.04	4.92	28.39	53.69		
BS/BV	BMI_under25	21.44	1.50	17.28	25.59		
	BMI_25to30	17.88	1.09	15.42	20.35	2.135	0.147
	BMI_over30	17.80	1.36	14.31	21.29		
Tb Pf	BMI_under25	−6.10	3.02	−14.49	2.29		
	BMI_25to30	−15.56	3.43	−23.33	−7.80	1.918	0.176
	BMI_over30	−17.30	4.61	−29.17	−5.44		
Tb Th	BMI_under25	0.19	0.01	0.17	0.22		
	BMI_25to30	0.24	0.01	0.21	0.26	3.069	0.071
	BMI_over30	0.22	0.01	0.18	0.26		
Tb N	BMI_under25	1.37	0.18	0.87	1.86		
	BMI_25to30	1.51	0.13	1.21	1.81	2.390	0.120
	BMI_over30	1.85	0.12	1.54	2.16		
Tb Sp	BMI_under25	0.56	0.04	0.45	0.67		
	BMI_25to30	0.52	0.03	0.44	0.59	3.512	0.052
	BMI_over30	0.41	0.04	0.29	0.52		
Porosity	BMI_under25	73.84	2.89	65.81	81.88		
	BMI_25to30	65.68	3.17	58.38	72.99	1.719	0.213
	BMI_over30	64.75	4.51	50.41	79.09		

BV/TV, bone volume fraction; BS/BV, specific bone surface; SMI, structure model index; Tb.Th, trabecular thickness; Tb.N, trabecular number; Tb.Sp, trabecular separation; Tb.Pf, trabecular pattern factor.

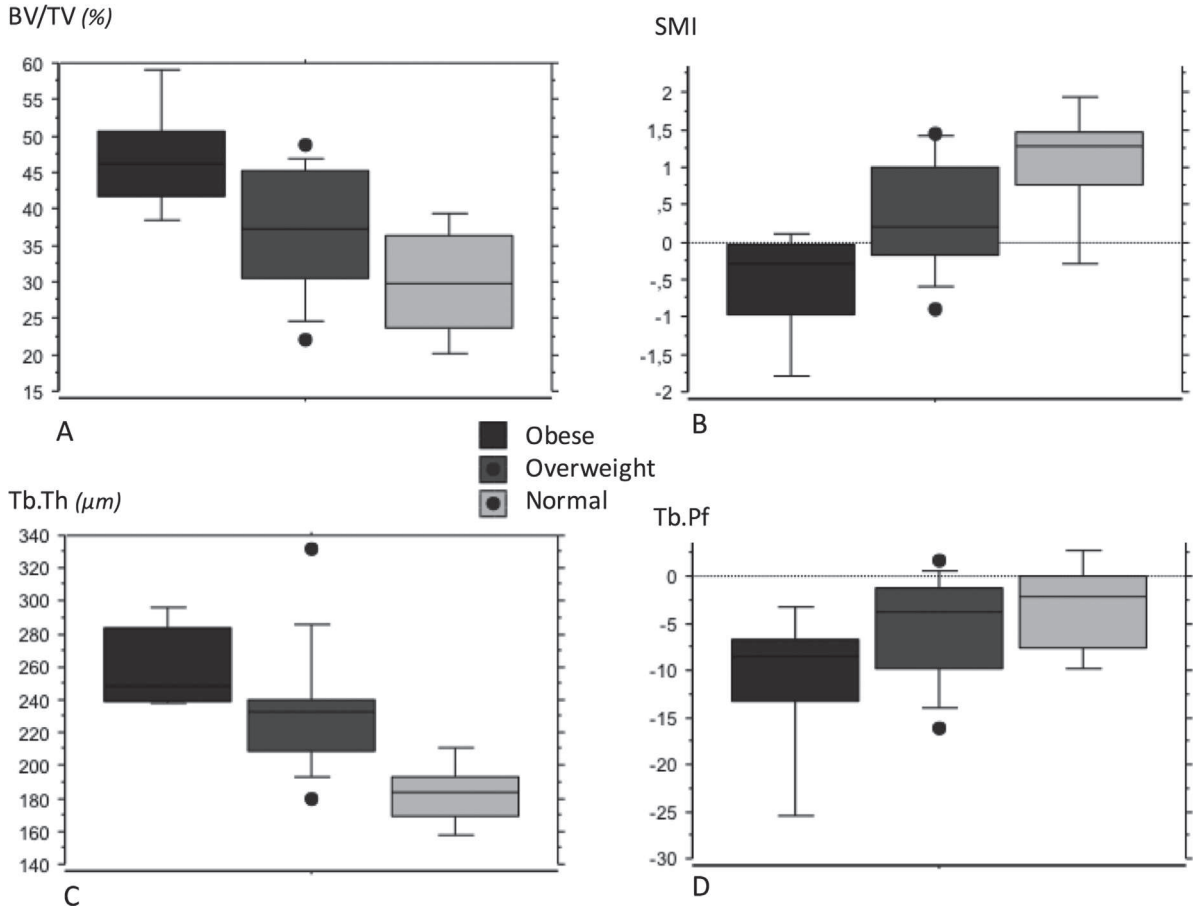


Figure 3. Box-plot for each body weight subgroup (normal, overweight, obese) for micro-CT parameters of the medial tibial plateau: bone volume fraction (BV/TV) (A), structure model index (SMI) (B), trabecular thickness (Tb.Th) (C), and trabecular pattern factor (Tb.Pf) (D).

Prospective studies have shown that obesity and excess weight are risk factors for knee osteoarthritis.[2,17,3] They are also risk factors for abnormal lower limb alignment, as this places excessive loads on the tibial plateaus.[5,20] These excessive loads, no matter the cause, induce premature cartilage wear, probably by direct action. However, the pathophysiology is more complex and involve many other indirect phenomena.[2] Studies have already related SCTB thickening and densification with cartilage deterioration in rabbit and mouse OA models.[21,22] Mechanically, there is a decrease in the SCTB modulus of elasticity in the tibial plateau of arthritic knees,[23] and some researchers have suggested that the lower SCTB modulus can increase cartilage stress and accelerate cartilage loss.[24] In an animal OA model[9] it has been shown that

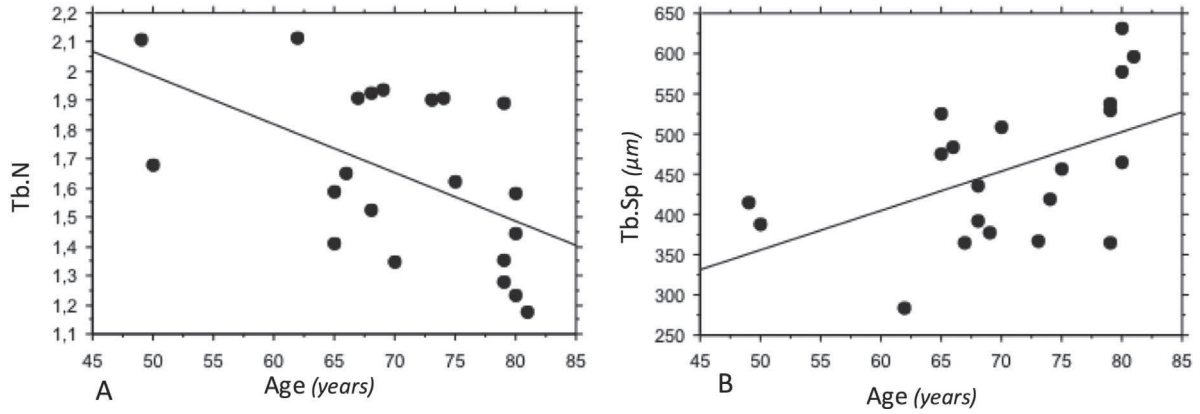


Figure 4. Correlation of age (years) with trabecular number (Tb.N) (A) and trabecular separation (Tb.Sp) (B) in the medial tibial plateau.

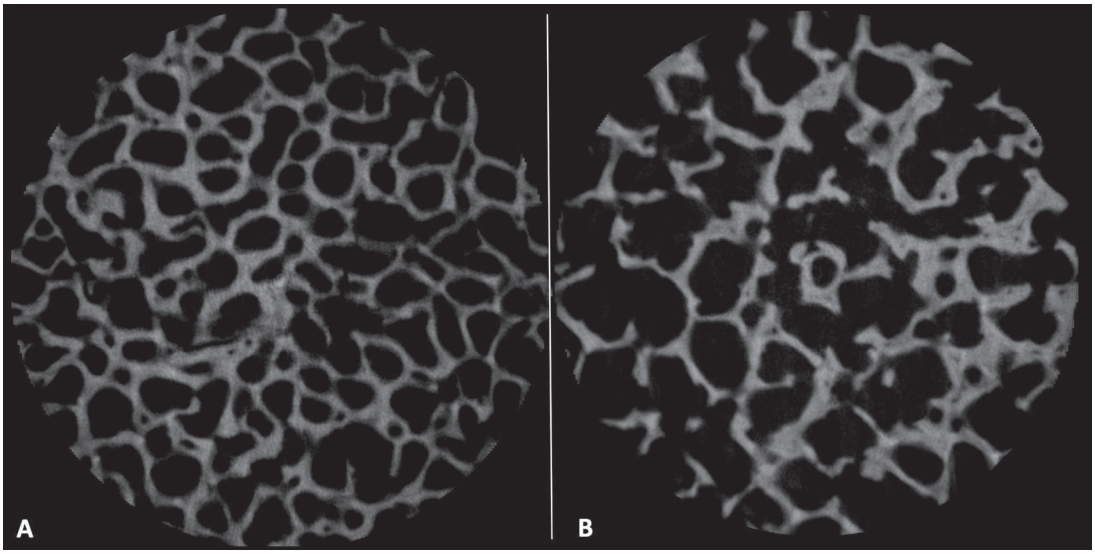


Figure 5. Micro-CT slices showing the effect of age on subchondral trabecular bone microarchitecture in the medial tibial plateau: (A) case 1, 49-year-old man with BMI of 23.5 and (B) case 16, 81-year-old man with BMI of 22.8

SCTB densification precedes chondrocyte apoptosis and cartilage degradation. This suggests that chondrocyte apoptosis could be a consequence of subchondral bone remodeling,[9] however the pathophysiology of this effect is not known. Articular cartilage and subchondral bone are a functional unit.[25] Any structural and biochemical changes in one structure will affect the homeostasis of the other.[11,26]

The current study confirms the intricacy of many phenomena in the appearance and development of osteoarthritis. The increase in the frequency of knee osteoarthritis with age[1] in the absence of other predisposing factors shows that physiological aging processes contribute to cartilage degeneration. The higher occurrence of knee osteoarthritis in overweight and obese individuals, or those with lower limb misalignment, shows that associated mechanical phenomena are important. The role of the subchondral bone in the initiation and progression of osteoarthritis has already been demonstrated.[2,17,27] Burr and Gallant[2] believe that subchondral bone densification is not the initiating factor for cartilage degradation and that it does not act in isolation to allow disease progression. The correlation between SCTB microarchitectural changes and weight and the demonstrated temporal relationship, in which SCTB densification precedes cartilage degeneration, may explain the higher frequency of knee osteoarthritis in younger, overweight patients.

AUTHORS' CONTRIBUTIONS

Credit for authorship should be based on: (i) substantial contributions to research design (N. Reina, E. Cavaignac, R. Pailhé, P. Swider), or the acquisition (A. Pailliser, N. Bonnevialle, N. Reina), analysis or interpretation of data (J.M. Laffosse, A. Pailliser, R. Pailhé, N. Reina); (ii) drafting the paper or revising it critically (J.M. Laffosse, N. Reina); (iii) approval of the submitted and final versions (J.M. Laffosse, A. Pailliser, N. Bonnevialle, R. Pailhé, N. Reina, E. Cavaignac, P. Swider).

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