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CLINICAL INVESTIGATIONS

Assessment of Bone Microarchitecture in Chronic Kidney Disease: A Comparison of 2D Bone Texture Analysis and High-Resolution Peripheral Quantitative Computed Tomography at the Radius and Tibia

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Abstract Bone microarchitecture can be studied noninvasively using high-resolution peripheral quantitative computed tomography (HR-pQCT). However, this technique is not widely available, so more simple techniques may be useful. BMA is a new 2D high-resolution digital X-ray device, allowing for bone texture analysis with a fractal parameter (H_{mean}). The aims of this study were (1) to evaluate the reproducibility of BMA at two novel sites (radius and tibia) in addition to the conventional site (calcaneus), (2) to compare the results obtained with BMA at all of those sites, and (3) to study the relationship between H_{mean} and trabecular microarchitecture measured with an in vivo 3D device (HR-pQCT) at the distal tibia and radius. BMA measurements were performed at three sites (calcaneus, distal tibia, and radius) in 14 healthy volunteers to measure the short-term reproducibility and in a group of 77 patients with chronic kidney disease to compare BMA results to HR-pQCT results. The coefficient of variation of H_{mean} was 1.2, 2.1, and 4.7% at the calcaneus, radius, and tibia, respectively. We found significant associations between trabecular volumetric bone mineral density and microarchitectural variables measured by HR-pQCT and H_{mean} at the three sites (e.g., Pearson correlation between radial trabecular number and radial H_{mean} $r = 0.472$, $P < 0.001$). This study demonstrated a significant but moderate relationship between 2D bone texture and 3D trabecular microarchitecture. BMA is a new reproducible technique with few technical constraints. Thus, it may represent an interesting tool for evaluating bone structure, in association with biological parameters and DXA.

Keywords Bone microarchitecture · Bone texture · Chronic kidney disease · HR-pQCT · Trabecular microarchitecture

The authors have stated that they have no conflict of interest.

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Areal measurement of bone mineral density (aBMD) by dual-energy X-ray absorptiometry (DXA) is the gold standard method to evaluate fracture risk. Nevertheless, up to 50% of fractures occur among individuals who would not be classified as osteoporotic based on DXA measurement [1, 2]. Thus, in 2000, the U.S. National Institute of Health defined new "quality" criteria for the diagnosis of osteoporosis in addition to a decreased bone mass. Bone strength is influenced not only by the amount of bone but also by its spatial distribution, cortical and trabecular microarchitecture, bone turnover, and material properties such as matrix mineralization, collagen polymorphisms, and microdamage. These quality criteria cannot be evaluated by DXA. Thus, new bone-imaging techniques have

been developed to assess bone microarchitecture parameters which may improve fracture risk prediction, including 2D bone-analysis (e.g., an X-ray-based fractal analysis or 2D analysis projection based on DXA images) and 3D techniques (e.g., quantitative computed tomography or magnetic resonance imaging) [3–5].

Peripheral quantitative computed tomography (pQCT), an X-ray-based technique, has been developed to measure separately trabecular and cortical density at peripheral sites. It allows the assessment of parameters of bone strength, such as polar moment of inertia, section modulus, and cortical thickness but not trabecular microarchitecture at the shaft of the radius and tibia [6]. This technique is not widely available in clinical practice. Recently, high-resolution pQCT (HR-pQCT) has been developed, with an isotropic voxel size of 82 μm, thus leading to a better resolution in comparison to previous pQCT devices [7]. HR-pQCT allows the measurement of both volumetric bone mineral density (vBMD) and microarchitectural parameters in total, cortical, and trabecular bone at the ultradistal radius and tibia, with low radiation exposure (effective dose of 3 μSv per measurement) with an acquisition time of 3 min. It has excellent precision for both density (0.7–1.5%) and structural parameters (1.5–4.4%), with similar results at the two sites [8]. However, despite these qualities, HR-pQCT measurements are limited to peripheral skeletal sites, and currently fewer than 20 devices are available worldwide.

Fractal analysis on conventional radiographs has been developed to evaluate bone biomechanical properties [9]. This texture analysis can characterize trabecular bone microarchitecture via 2D projection images (gray-level projection) and the calculation of a fractal parameter (H_{mean}). In cross-sectional analyses, bone texture analysis was independent of BMD for determining the risk of fracture [10]. A 2D high-resolution digital X-ray device (BMA) was recently proposed as an improvement of this general concept [11]. BMA provides better precision of bone texture parameters than previously found on digitized films, with a low radiation exposure (effective dose of 3 μSv/measurement) [11]. Previous studies which have evaluated this technique at the calcaneus found a significant decrease of H_{mean} with age [11]. It would therefore be interesting to evaluate texture analysis at other peripheral sites, such as the radius and tibia, to try to improve fracture risk prediction since other bone-imaging techniques (e.g., HR-pQCT, magnetic resonance imaging) have also been described at these sites [8, 12].

Thus, the aims of this study were (1) to evaluate the reproducibility of BMA at two novel sites (distal radius and tibia) in addition to the conventional site (calcaneus), (2) to compare the results obtained with BMA at all of those sites, and (3) to study the relationship between the texture analysis (fractal parameter, H_{mean}) obtained with BMA and trabecular microarchitecture measured with a 3D device (HR-pQCT) in a cross-sectional analysis of patients with chronic kidney disease (CKD) who were known to have sizeable architectural impairment.

Patients and Methods

Subjects

The study was approved by a local independent ethical committee (Comité de protection des personnes Lyon Sud-Est II), and all patients gave written informed consent before participation. To assess the short-term reproducibility of BMA analysis, 14 healthy volunteers (aged 20–37 years) underwent three separate scans of the distal radius, tibia, and calcaneus within a 1-month period. The first and second measurements were performed the same day after repositioning; the third measurement was performed 1–2 weeks after, as previously recommended by Gluer et al. [13].

To assess the correlation between 2D and 3D devices, we performed BMA and HR-pQCT measurements in a group of CKD patients as CKD is associated with important bone-quality impairment [14].

HR-pQCT

vBMD and trabecular microarchitecture were assessed at the ultradistal radius and tibia using an HR-pQCT system (XtremeCT; Scanco Medical, Brüttisellen, Switzerland). This system enables the simultaneous acquisition of a stack of 110 parallel slices with a nominal resolution (voxel size) of 82 μm [8], leading to a dimensional representation of approximately 9 mm in the axial direction. The following settings were used: effective energy of 60 kVp, X-ray tube current of 95 mA, and matrix size of 1,536 * 1,536 pixels. Positioning and detailed technical settings were previously described [8]. Briefly, the measurement region was manually defined on an anteroposterior scout view, with a reference line at the joint surface of the radius and tibia, as shown in Fig. 1. Then, the first slice was 9.5 and 22.5 mm proximal to the reference line for the distal radius and tibia, respectively. The outcome variables used in our analyses included vBMD (mg HA/cm^3) for entire (D_{tot}) and trabecular (D_{trab}) regions and trabecular thickness (Tb.Th, μm), number (Tb.N, mm^{-1}), separation (Tb.Sp, μm), and intraindividual distribution of separation (Tb.SpSD, μm).

BMA Analysis

As illustrated in Fig. 2, images were obtained at three sites: calcaneus, distal tibia, and distal radius. This system (D3A Medical Systems, Orléans, France) enables the acquisition

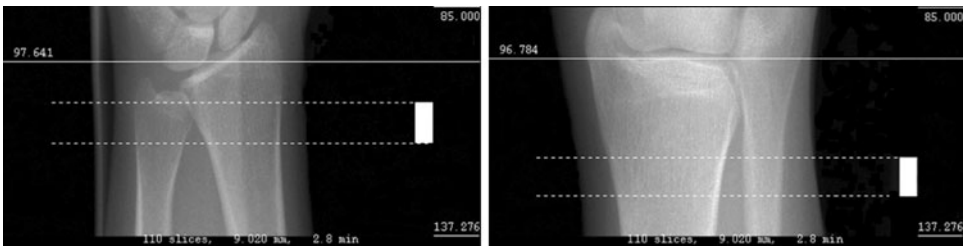

Fig. 1 Positioning of the ROI at the tibia and the radius with HR-pQCT. Scout views demonstrating the reference line position (*solid line*) and the measurement site (between *dotted lines*). The first CT slice was 9.5 and 22.5 mm proximal to the reference line for the distal radius and distal tibia, respectively

of an image with a nominal resolution (pixel size) of 50 μm [11]. A first acquisition was performed in all subjects with the same technical settings (calcaneus 55 kV, 10 mAs; distal tibia 55 kV, 20 mAs; and distal radius 50 kV, 12 mAs). Then, for each site the region of interest (ROI) was positioned and the mean gray level was calculated within the ROI. If the mean gray level within the ROI was out of range, a second acquisition with an accordingly corrected intensity was then performed.

At the calcaneus, two anatomical landmarks were manually placed by the operator to position an ROI of 256 * 256 pixels [11]. At the distal tibia (radius), the anatomical landmarks were manually placed to obtain a tangent line to the middle of the tibia (radius) joint surface, and then a horizontal translation of 440 pixels/22 mm (180 pixels/9 mm) was applied to position the 256 * 180-pixel ROI so that we studied the same region as HR-pQCT measurement (Fig. 2).

The methods used to calculate the fractal parameter (H_{mean}) have been previously described in detail by Lespessailles et al. [11]. Briefly, the gray levels of the ROI were fitted to a fractal model for texture analysis, the fractional Brownian motion, which allows description of fractal shapes by a single parameter, H. For each ROI, H_{mean} was averaged based on the evaluation of H in eight different directions following a 22.5° step. The higher the H_{mean}, the smaller the roughness of the texture within the ROI. In texture analysis, roughness is a parameter that quantifies both the amplitudes and frequencies of the irregularities of a surface. In BMA application, the texture basis is given by the soft tissues and the irregularities are represented by trabecular elements. In clinical practice, the higher the H_{mean}, the better the trabecular status.

For both BMA and HR-pQCT, examinations were performed at the nondominant radius and at the right tibia, except when there was a fracture history at these sites.

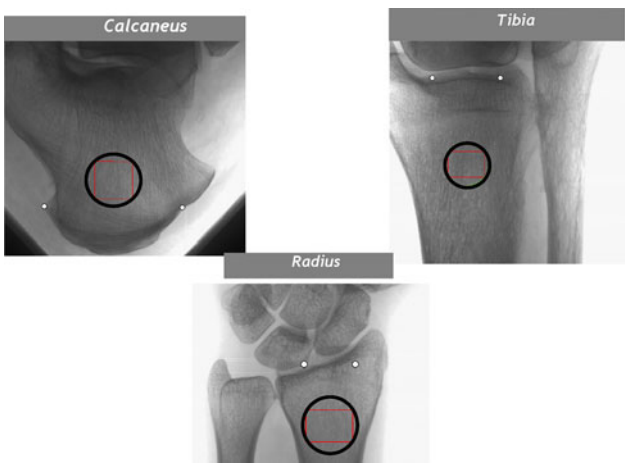

Fig. 2 Positioning of the ROI at the three sites (BMA). ROIs are the *circled regions*. At the calcaneus, it was positioned as recommended by the manufacturer. At the radius and tibia, ROIs were set so that they matched the ROIs used in HR-pQCT

Quality Control

Calibration tests were carried out every day for the two techniques using an external phantom to detect any potential drift of the instrumentation. We did not observe any drift during the period of the protocol. Both examinations (BMA and HR-pQCT) were analyzed by the same observer (J. B.).

Statistical Analysis

For each subject in the reproducibility study, a coefficient of variation (CV) was calculated as the standard deviation of the three repeated measurements divided by the subject mean. Furthermore, the short-term precision errors were then calculated as root-mean-square (RMS) averages of the precision errors for each of the subjects. Relationships between the fractal parameter, vBMDs, and microarchitecture were estimated using Pearson or Spearman correlations, depending on the distribution of variables (i.e., Pearson for parametric distribution, Spearman for non-parametric distribution). Comparison of H_{mean} measured at the radius, tibia, and calcaneus was performed by repeated-measures ANOVA, followed by Tukey's test for pairwise comparisons. The statistical level of significance was 0.05.

All statistical analyses were performed with SPSS software (version 15.0; SPSS, Inc., Chicago, IL).

Results

Characteristics of CKD Patients

We performed BMA and HR-pQCT measurements in a group of 77 CKD patients (50 men and 27 women, mean age 67 ± 15 years, mean glomerular filtration rate [GFR] 33 ± 12 mL/min per 1.73 m^2, body mass index 26.0 ± 4.6 kg/m^2). Among these individuals, 13 had a history of fractures and 18 suffered from type 2 diabetes mellitus. Due to patient motion during the examinations, BMA measurements at the calcaneus and tibia could not be analyzed in four patients and in one patient at the radius; for the same reason, HR-pQCT measurements could not be analyzed in four patients at the radius and in two at the tibia. Thus, this results in 76, 73, and 73 BMA measurements (at the radius, tibia, and calcaneus, respectively) and 73 and 75 HR-pQCT scans (at the radius and tibia, respectively).

Biochemical assessments of phosphate/calcium parameters were as follows: serum calcium 2.31 ± 0.13 mmol/L, phosphate 1.18 ± 0.21 mmol/L, parathyroid hormone 99 ± 97 pg/L, 25 OH vitamin D 22 ± 14 ng/L, and total alkaline phosphatase 77 ± 26 IU/L.

Reproducibility of the Fractal Parameter with BMA

As summarized in Table 1, reproducibility was good at all sites, mainly at the calcaneus and radius (CV = 1.2 and 2.1%, respectively), with slightly less satisfying values at the tibia (4.7%). The CV and its 95% confidence interval (CI) for each site are also summarized in Table 1.

Comparison of the Fractal Parameter Obtained at Different Sites

Mean values of H_{mean} among our 77 CKD patients were 0.609 ± 0.038 at the radius, 0.562 ± 0.044 at the tibia, and 0.621 ± 0.024 at the calcaneus, as summarized in Fig. 3. When analyzing H_{mean} at the three sites, there was a significant association between the tibia and calcaneus ($r = 0.437$, $P < 0.001$, $n = 69$) and between the tibia and radius ($r = 0.564$, $P < 0.001$, $n = 71$) but not between the radius and calcaneus ($n = 71$).

Table 1 Precision of texture analysis (fractal parameter H_{mean}) at three different sites with BMA, calculated from three repeated measurements with repositioning in 14 healthy volunteers

	Mean ± SD	CV (%, 95% CI)
Calcaneus	0.627 ± 0.024	1.17 (0.92–1.58)
Tibia	0.528 ± 0.036	4.66 (3.70–6.30)
Radius	0.584 ± 0.033	2.08 (1.65–2.82)

Comparison Between BMA Analysis and HR-pQCT

As summarized in Table 2 and in Fig. 4, we found significant correlations between all trabecular parameters (density and microarchitecture) and the fractal value at the three sites except for tibial trabecular thickness, which did not correlate with H_{mean} at any site. The relationships observed between the two techniques were stronger at the same site, especially at the tibia ($r > 0.5$). The trend was similar when comparing HR-pQCT and BMA measurement at the radius. When comparing H_{mean} at the calcaneus with trabecular microarchitecture measured with HR-pQCT at the tibia and the radius, we also observed a relationship, though of lower significance.

Moreover, there were significant relationships between trabecular microarchitecture assessed with HR-pQCT at the two sites, ranging from 0.585 (for trabecular thickness) to 0.871(for trabecular density), with all P values <0.001 ($n = 71$).

BMA Results in CKD Patients According to the History of Fractures

When comparing the 13 patients with history of fractures to the other CKD patients, there were no significant differences regarding age (69 ± 9 vs. 67 ± 16 years, P = nonsignificant [NS]), BMI (24.7 ± 4.4 vs. 26.4 ± 4.6 kg/m^2, P = NS),

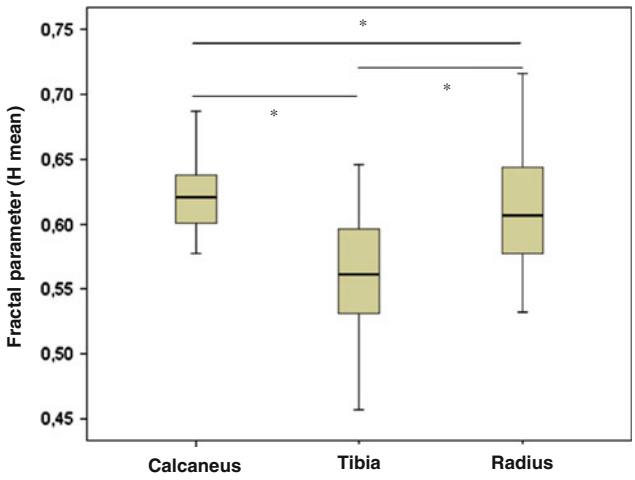

Fig. 3 Graphic representation of the different H_{mean} values obtained at the three sites in CKD patients. * $P < 0.001$. H_{mean} values measured at the radius, tibia, and calcaneus were compared by repeated measures ANOVA, followed by Tukey's test for pairwise comparisons

Table 2 Correlation between the fractal parameter (BMA) and microarchitectural and density parameters (HR-pQCT)

HR-pQCT	H_{mean}		
	Calcaneus	Tibia	Radius
Tibia			
D_{trab}	0.420**	0.532**	0.445**
Tb.N	0.319**	0.512**	0.437**
Tb.Sp	−0.377**	−0.552**	−0.415**
Tb.SpSD	−0.362**	−0.537**	−0.426**
Tb.Th	0.236	0.184	0.140
Radius			
D_{trab}	0.365**	0.503**	0.537**
Tb.N	0.275*	0.436**	0.472**
Tb.Sp	−0.347**	−0.492**	−0.472**
Tb.SpSD	−0.325**	−0.355**	−0.403**
Tb.Th	0.317**	0.412**	0.480**

Spearman or Pearson correlation according to the distribution of variables

Number of patients analyzed for each correlation: H_{mean} calcaneus and HR-pQCT tibia $n = 69$; H_{mean} calcaneus and HR-pQCT radius $n = 68$; H_{mean} tibia and HR-pQCT tibia $n = 70$; H_{mean} tibia and HR-pQCT radius $n = 68$; H_{mean} radius and HR-pQCT tibia $n = 72$; H_{mean} radius and HR-pQCT radius $n = 70$

* $P < 0.05$, ** $P \leq 0.01$

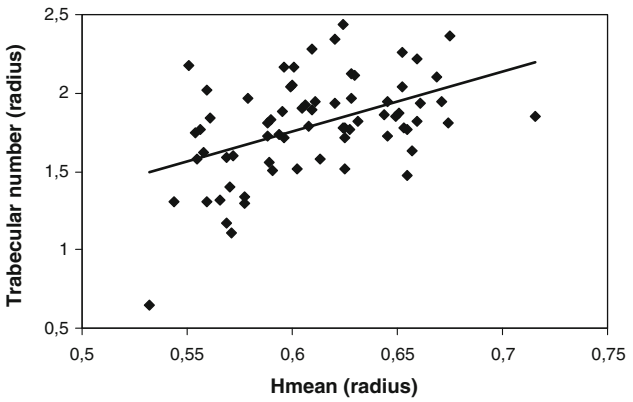

Fig. 4 Correlation between H_{mean} at the radius (BMA) and trabecular number at the radius (HR-pQCT): $r = 0.472$, $P < 0.001$

GFR (31 ± 11 vs. 32 ± 12 mL/min per 1.73 m^2, P = NS), proportion of diabetes mellitus (23 vs. 24%, P = NS), and proportion of men (46 vs. 68%, P = NS). However, H_{mean} at the calcaneus (0.611 ± 0.014 vs. 0.623 ± 0.025, $P = 0.024$) was significantly lower in CKD patients with a history of fractures, with a similar trend at the radius (0.592 ± 0.038 vs. 0.613 ± 0.038, $P = 0.068$). By contrast, results were not significant at the tibia. Concerning HR-pQCT, we found significant decreased total BMD (257 ± 52 vs. 299 ± 71 mgHA/cm^3, $P = 0.05$), trabecular BMD (137 ± 53 vs. 174 ± 44 mgHA/cm^3, $P = 0.015$), and trabecular thickness (67 ± 10 vs. 79 ± 13 μm, $P = 0.004$) in the fractured CKD patients at the tibia; results were similar at the radius.

Discussion

In this study we applied the measurement of the fractal parameter H_{mean} with BMA at two novel sites (tibia and radius) and at the conventional site (calcaneus) and assessed their relationship with trabecular microarchitecture measured at the distal radius and tibia by HR-pQCT. Thus, the main findings of the present study are (1) the good reproducibility of H_{mean} assessment at the three sites; (2) a significant association between the results of bone texture analysis at the tibia and the calcaneus, on the one hand, and at the tibia and the radius, on the other hand; and (3) the association between trabecular microarchitecture assessed with HR-pQCT and H_{mean} at the three sites.

The reproducibility of H_{mean} at the calcaneus was similar to that reported by Lespessailles et al. [11], who found a CV of 1.2%. At the radius, the CV of BMA measurement was similar to that provided by DXA for the measurement of aBMD (1–2%) or HR-pQCT (0.7–1.5% for density and 0.9–4.4% for structural parameters). The results were slightly lower at the tibia (4.7%), comparable to the upper values found with HR-pQCT, likely due to a more difficult positioning of patients. Thus, the most reproducible site for measuring H_{mean} appears to be the calcaneus. Since the results of reproducibility are satisfying at the radius when compared to other imaging techniques, the use of both the radius and the calcaneus to assess H_{mean} could represent a valuable option to improve the evaluation of bone status with BMA.

As illustrated in Fig. 3, the H_{mean} values obtained at the three sites were significantly different. This apparent discrepancy could be explained by the differences in BMA and structure at these three sites, as previously described, e.g., with magnetic resonance imaging [15].

We found a moderate correlation between the BMA texture parameter and HR-pQCT microarchitectural variables, similar to Chappard et al. [16], who demonstrated a good relationship between 2D texture analysis on radiographs and trabecular histomorphometry. All of these results are consistent with the fact that H_{mean} was developed to be an index of the 3D trabecular microarchitecture, which is not addressed by DXA. We can therefore hypothesize that H_{mean} at all sites could be independent of total aBMD but correlated to trabecular BMD and microarchitecture, as illustrated in Table 2. Thus, since it has been well demonstrated that trabecular structure or texture parameters of the radius or the calcaneus could help to identify spine and hip fractures [17–19], BMA

measurement could represent a new tool to improve the prediction of fracture risk; however further longitudinal studies are required to test this hypothesis.

A first limitation of this study is its focus on CKD patients, who usually experience bone damage as soon as their GFR falls below 60 mL/min per 1.73 m^2 [14]. Indeed, the impact of CKD on bone and mineral status may be immediate (serum phosphocalcic dysequilibrium) or delayed (fractures, vascular calcifications); in hemodialysis patients there is a fourfold increased risk of hip fracture [20], whereas there is a twofold increased risk of hip fracture in predialysis patients [21]. Even if several studies have reported on DXA in CKD patients with contradictory results [14, 22–24], recent international guidelines have emphasized the fact that BMD assessment by DXA analysis should no longer be performed in CKD patients since it does not predict fracture risk in this population and does not predict the type of renal osteodystrophy [25].

Several studies have been performed in CKD patients with a pQCT device that measures separately trabecular and cortical BMD at peripheral sites but does not assess trabecular microarchitecture. Studies on dialysis patients usually have reported decreased cortical vBMD and thickness compared to controls, without significant changes in trabecular vBMD [26–29]. All of these studies confirmed a cortical impairment, probably due to secondary hyperparathyroidism, often seen during end-stage renal disease. In predialysis patients, Obatake et al. [30] reported a decrease in total, cortical, and trabecular BMD in 53 CKD patients after a 1-year follow-up. In 2005, Tsuchida et al. [31] reported a negative correlation between trabecular BMD and biomarkers of bone formation in 85 predialysis patients. To our knowledge, no studies have evaluated bone status with bone texture analysis in CKD patients and only two studies have focused on this topic with HR-pQCT. Nickolas et al. [32] recently reported a more important trabecular loss and decreased BMD in 32 predialysis CKD patients with a history of fractures in comparison to 59 CKD patients without fractures, similar to our present results that are, however, from cross-sectional data. The second study evaluating the interest of HR-pQCT during CKD was performed in the present cohort of CKD patients, studied in comparison to the epidemiological cohorts STRAMBO and OFELY: we demonstrated that these predialysis CKD patients experienced a moderate but significant trabecular impairment, positioning their results between those of normal and osteopenic controls [33].

Moreover, when comparing our results obtained with BMA to results obtained in a case–control, multicenter study evaluating bone texture analysis in osteoporosis in 219 controls (mean age 69 ± 10 years) and 159 osteoporotic postmenopausal women [34], CKD patients had H_{mean} values between those of healthy controls and osteoporotic patients with fractures (0.609 ± 0.038 vs. 0.612 ± 0.031 vs. 0.600 ± 0.035, respectively).

The present study consisted of a preliminary approach to BMA measurement, to determine its reproducibility at three sites and to study its relationship with 3D bone evaluation by HR-pQCT in a specific population of patients. Even if the data on our CKD patients seem close to both HR-pQCT and BMA values of controls having similar age and gender, these results need to be replicated in a cohort of individuals with normal renal function. Unfortunately, BMA reference values were not available at our center to locally compare the results observed in our CKD patients to those of healthy controls.

Moreover, this study is also limited by its cross-sectional design, which prevented us from examining the predictive value for incident fracture of the texture parameter. The association we found between architectural variables assessed using HR-pQCT and H_{mean}, on the one hand, and the observation of a significant decrease of H_{mean} at the calcaneus and probably an almost significant decrease at the radius in CKD patients with a history of fractures, on the other hand, can justify prospective studies testing the ability of texture analysis to predict fracture better than aBMD alone as it is associated with bone microarchitecture.

In conclusion, this study demonstrated the feasibility of H_{mean} measurement with BMA at two novel sites. However, the precision error was the lowest at the calcaneus. We also found a significant association between H_{mean} measurement and 3D trabecular microarchitecture measured by HR-pQCT at the same site. Thus, BMA measurement might be a promising simple tool for evaluating trabecular bone, but its ability to predict the risk of fracture should be evaluated in further longitudinal prospective studies.

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