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ORIGINAL ARTICLE

Trabecular bone score to assess bone microarchitecture in end-stage renal disease patients

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Abstract

Summary Rationale: This study evaluates TBS for estimating bone microarchitecture in ESRD patients using HR-pQCT as the reference technique. Main results: TBS correlates significantly with vBMD and bone microarchitecture, unlike aBMD. Significance: TBS may complement bone health assessment in ESRD patients by offering additional information alongside aBMD.

Purpose Given the high fracture risk, non-invasive techniques for assessing bone fragility in chronic kidney disease (CKD) remain important. Trabecular bone score (TBS) may provide additional information that could help guide treatment and follow-up decisions. The aim of this study is to investigate whether TBS reflects bone microarchitecture in end-stage renal disease (ESRD) patients, using high-resolution peripheral quantitative computed tomography (HR-pQCT) as the reference technique. Additionally, we aim to identify parameters associated with a low TBS.

Methods Seventy-five ESRD patients were included at the time of kidney transplantation (KTx). Areal bone mineral density (aBMD) was analyzed using dual-energy X-ray absorptiometry (DXA). TBS was assessed from the L1-L4 area during DXA. Volumetric BMD (vBMD) and bone microarchitecture at tibia and radius sites were analyzed using HR-pQCT.

Results In ESRD patients, those with TBS < 1.370 were older and had a higher body mass index (BMI). In contrast to T-score-based classification (≤ -2.5 or > -2.5), low TBS was linked to significantly lower trabecular and cortical vBMD, reduced trabecular bone volume fraction (BV/TV) and trabecular number (Tb.N), and increased trabecular separation (Tb.Sp). In multivariate analysis, older age, higher BMI, and lower Tb.N remained independently associated with low TBS, while no HR-pQCT parameters were linked to low aBMD (T-score ≤ -2.5).

Conclusion TBS correlates with both trabecular and cortical parameters measured by HR-pQCT, potentially offering a complementary perspective on bone microstructure compared to aBMD. At the time of KTx, a low TBS appears to better discriminate patients with significantly lower vBMD than aBMD alone.

Keywords Trabecular bone score (TBS) · End-stage renal disease (ESRD) · Bone microarchitecture · High-resolution peripheral quantitative computed tomography (HR-pQCT)

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Introduction

Bone disease in end-stage renal disease (ESRD) patients is complex. Patients with chronic kidney disease (CKD)-associated osteoporosis exhibit reduced bone volume, mineralization defects, and altered microarchitecture, especially with increased cortical porosity compared to non-CKD patients [1–3]. Accordingly, the risk of fracture in ESRD patients is 3–5 times higher than in the general non-CKD population [4–6]. The Kidney Disease Improving Global Outcome (KDIGO) guidelines now recommend systematic bone densitometry in ESRD patients [7], but the ability of dual-energy X-ray absorptiometry (DXA) scan to predict fracture risk is far from ideal [8].

In the general population, a substantial proportion of fragility fractures occur in patients without densitometric osteoporosis [9, 10]. Studies have demonstrated that in patients older than 65 years, only 10 to 44% of fractures occur in those with a T-score lower than −2.5 [11]. In CKD patients, the same assumptions are made: indeed, the 2D projection of DXA fails to capture cortical and trabecular compartments, and in CKD patients as in the general population, bone mineral density (BMD) assessment can be challenging because of frequent scoliosis and osteoarthritis at the lumbar spine (LS) [12]. Additionally, the underlying metabolic bone diseases, such as renal osteodystrophy with impaired mineralization and altered turn-over, further increase the risk of fracture independently of DXA-based BMD measurement [13]. Accurate determination of the type of bone disorders in CKD patients requires a bone biopsy, but this invasive procedure is rarely performed [14]. Non-invasive methods, such as high-resolution peripheral quantitative computed tomography (HR-pQCT), have become available for assessing total (Tt), cortical (Ct) and trabecular (Tb) volumetric BMD (vBMD) and microarchitecture (bone geometry and structure). Because HR-pQCT measures vBMD rather than areal BMD (aBMD), it avoids projection artefacts resulting from differences in bone size that are inherent to DXA [15, 16]. Recent studies in the general population have demonstrated that Ct and Tb vBMD and microarchitecture are independent predictors of incident fracture risk [17]. In ESRD patients, a meta-analysis shows that patients under dialysis have lower Tt, Ct vBMD, altered geometry (thinner cortical bone), and deterioration of the trabecular network [18].

The trabecular bone score (TBS) is an index of bone microarchitecture, derived from the LS DXA scan. TBS is evaluated by determining the variogram of the trabecular bone projected image, calculated as the sum of the squared gray-level differences between pixels at a specific distance and angle. TBS is then calculated as the slope of the log–log transform of this variogram. The mean value of the individual measurements for L1–L4 represents the LS TBS [19]. A homogeneous microarchitecture results in a higher TBS value, whereas a more heterogeneous microarchitecture results in a lower TBS value. In the general population, TBS enhances the ability of DXA to predict fracture risk [20] and improves fracture risk prediction [21–24]. A recent meta-analysis demonstrated that, compared to a non-CKD population, the TBS level was significantly lower in dialysis patients [25]. Even if a clear cut-off for TBS in evaluating fracture risk is not well established, some studies demonstrate the ability of a low TBS (below 1.370) to predict fragility fractures independently of BMD in kidney transplant recipients (KTRs) and non-dialysis CKD patients [26, 27]. It is crucial to distinguish between bone quantity, measured by DXA, and bone quality, assessed by TBS and HR-pQCT, as both factors significantly contribute to overall bone health and fracture risk.

As part of a prospective trial (NCT04713774) on diagnosing and monitoring bone diseases in newly KTRs, we measured aBMD, TBS, and HR-pQCT parameters in ESRD patients on the day of kidney transplantation (KTx). Our goal was to determine whether TBS correlates more closely than aBMD with bone microarchitecture parameters measured by HR-pQCT.

Research design and methods

Patients

All patients referred for a single KTx at the University Hospital of Liège with no history of exposure to antiresorptive agents were eligible for inclusion in this prospective cohort study (NCT04713774). The study was approved by the local ethics committee (CHU ULiège B707201940317) an all patients provided written informed consent. Patients were included from February 2020 to September 2023.

Parameters and detailed patient history were prospectively collected and subsequently analysed for the study, including age, gender, body mass index (BMI), cause of kidney failure, time on dialysis before transplantation, history of previous fractures, and history of diabetes. Parathyroidectomy and/or calcimimetic use before KTx were also considered.

Laboratory measurements were conducted after a fasting period within 12 h prior to the KTx. Routine chemistry analytes (total and ionized calcium, phosphate, bicarbonates, and creatinine) were measured using standard laboratory techniques. Serum 25-hydroxy-vitamin D (calcidiol) and derived were measured using Liquid Chromatography-Tandem Mass

Spectrometry (LC–MS/MS). Bone turnover biomarkers have been evaluated, such as serum concentrations of full-length (biointact) parathyroid hormone (PTH) measured using a third-generation kit from DiaSorin® on the Liaison platform, via an immunoradiometric assay (IRMA). Bone alkaline phosphatase (BALP), procollagen type 1 N-terminal propeptide (P1NP), tartrate-resistant acid phosphatase-5b (TRAcP-5b) and C-telopeptides were analyzed using the iSYS automated analyzer from Immunodiagnostic Systems (IDS). Sclerostin levels were performed on the Liaison platform with the Diasorin® specific kit. All were measured using enzyme-linked immunosorbent assay kits according to the manufacturer's directions and performed locally and centralized in the Clinical Chemistry Department of CHU Sart Tilman, accredited against the ISO 15189.

DXA, TBS and HR-pQCT imaging

Participants underwent baseline BMD measurements by DXA (QDR-4500 Discovery; Hologic, Waltham, MA, USA), at the LS, femoral neck (FN), and total hip (TH). aBMD values were expressed in g/cm^2 and as T-scores. Osteoporosis was defined as an aBMD T-score at the LS, FN, or TH of −2.5 or less [28]. TBS evaluation derived from pixel grey scale texture variations in the L1-L4 LS images acquired by DXA [19] [TBS iNsight Software (version 3 (TBS-V3); Medimaps, Merignac, France)]. Even though a universally accepted cut-off for TBS in evaluating fracture risk is not well established in CKD patients, some studies have highlighted the ability of a low TBS to predict fragility fractures independently of BMD in CKD and KTRs. In this study, we used a TBS threshold of 1.370 to define low versus high TBS values, based on the findings of Naylor et al. [26]. Aleksova et al. [27] also examined TBS in CKD patients at the time of KTx and proposed an alternative cut-off of 1.31 for fracture risk assessment, but its findings were based on a smaller sample size. Given these considerations, we conducted additional analyses using both the 1.370 and 1.310 thresholds to ensure robustness and consistency in our results. TBS measurements in patients with BMI ≥ 35 kg/m^2 and due to artefact analysis ($n = 2$) were not validated by the software. A sensitivity analysis was conducted using the new pre-market TBS software (version 4.0, Core Module (TBS-V4)), which features an improved algorithm adjusting for directly measured abdominal soft tissue thickness. This enhancement addresses limitations in earlier versions, such as V3, which relied on BMI as a surrogate for soft tissue thickness [29]. The updated algorithm has demonstrated comparable performance to previous versions in predicting fragility fractures [29] and is equally or more effective in monitoring changes in TBS following antiresorptive and anabolic osteoporosis therapies [29]. However, the TBS-V4 is under regulatory review for clinical application, and therefore currently remains confined to the research domain.

HR-pQCT images of the distal radius and distal tibia (non-dominant, non-fractured limb) were obtained using the XtremeCT device with standard protocols (XtremeCT II, version B (SN1802101); Scanco Medical AG, Bruttisellen, Switzerland). vBMD values were expressed in milligrams of hydroxyapatite per cubic centimeter (mg HA/cm^3).

Statistical analysis

Data were presented as mean ± standard deviation (SD) when the distribution was normal and as median with interquartile range (quartile 1 – quartile 3) when it was not. Normality was assessed using the Shapiro–Wilk test. For comparison of variables across groups, one-way analysis of variance, or the Kruskal–Wallis rank sum test, were used for normally distributed and skewed variables, respectively. For dichotomous and categorical variables, chi-square or Fisher's exact tests were used. Spearman's rank correlation was used to assess the univariate relationship between TBS and HR-pQCT parameters.

To study the risk of having a TBS < 1.370 at the time of KTx as a function of other parameters, the logistic regression model was used. The models were done at the univariate level and then at the multivariate level with stepwise selection by considering parameters whose p-values were less than 0.05 in univariate analyses. We report the odds ratio (OR) and the 95% confidence intervals (CI) as well as the p-values for multivariate models. The results were considered significant at the 5% uncertainty level ($p < 0.05$).

The sensitivity analysis was conducted using the TBS values generated with the TBS-V4. We measured the absolute differences in TBS between the V3 and uncalibrated V4 versions, and evaluated the correlations between them. The intraclass correlation coefficient (ICC) was also calculated to assess the reliability and agreement between the two versions.

The calculations were carried out using SAS version 9.4 (SAS Institute, Cary, NC, USA) and Stata IC version 16.1 (StataCorp, College Station, TX, USA).

Results

Seventy-five ESRD patients were included. Clinical and biological characteristics of the population are summarized in Table 1. Median age was 60.4 [52.1 – 65.8] years old, and 70.7% were male. The leading cause of CKD was glomerular disease (30.7%) followed by diabetic (13.3%) and vascular nephropathy (12%). Past medical history of diabetes and hypertension was found in 25.3% and 90.7%, respectively. Sixteen percent were on active vitamin D and

Table 1 Clinical and biological characteristics of the population at the time of transplantation ($n = 75$)

Recipients		
	Age (years)	60.4 [52.1 – 65.8]
	Gender (% male)	70.7
	BMI (kg/m^2)	26.2 ± 4.6
	ESRD causes (%)	Glomerular disease 30.7 Diabetic 13.3 Genetics 13.3 Vascular 12 Others 30.7
	Rank KTx (% first KTx)	92
	Time on dialysis before KTx (months)	31.5 [19.1 – 45.7]
	Time from inscription to KTx (months)	11.2 [5.3 – 25.5]
	Haemodialysis (%)	76.8
	History of parathyroidectomy prior to KTx (%)	2.7
	On calcimimetics prior to KTx (%)	18.7
	Major fracture prior to KTx (%)	9.3
	Any fracture prior to KTx (%)	34.7
Biological parameters	25-OH VitD (ng/mL)	39.2 ± 12.6
	PTH (ng/L) [4–33]	136 [71—241]
	c-telopeptides (ng/L) [< 695]	1293 [728 – 2433]
	P1NP (µg/L) [12.8 – 71.9]	90.7 [49.6 – 135.1]
	BALP (µg/ L) [5.5 – 22.9]	12.9 [10.3 – 21.3]
	TRAcP-5b (U/L) [1.4 – 6.1]	5 [3.4 – 6.7]
	Sclerostin (ng/mL) [0.25 – 1.13]	1.05 [0.62 – 1.64]
	Ionized Calcium (mmol/L) [1.15 – 1.33]	1.15 [1.09 – 1.21]
	Total Calcium (mmol/L) [2.2 – 2.6]	2.34 ± 0.17

Values are presented either as median [IQR] or mean ± SD depending on the distribution

Normal values of biological parameters are indicated between brackets

25-OH-vitD 25-hydroxy-vitamin D, *BALP* bone alkaline phosphatase, *BMI* body mass index, *ESRD* end stage renal disease, *IQR* interquartile range, *KTx* kidney transplantation, *P1NP* procollagen type 1 N-terminal propeptide, *PTH* parathyroid hormone, *SD* standard deviation, *TRAcP-5b* tartrate-resistant acid phosphatase-5b

18.7% on calcimimetic at the time of KTx. Time on dialysis before receiving a KTx was 31.5 [19.1 – 45.7] months. Seventy-five percent were treated by haemodialysis and 20% by peritoneal dialysis. Five percent of the patients were transplanted before starting dialysis. At the time of KTx, 34.7% of patients had a history of fractures, including 9.3% with a history of major osteoporotic fractures (MOFs), defined as hip, humerus, forearm, or clinical vertebral fractures (Table 1). Results of bone biomarkers are given in Table 1. 25-OH vitamin D concentrations was 39.2 ± 12.6 ng/mL. Median PTH level at the time of KTx was four times the upper limit of normal (136 [71 – 241] ng/L).

All DXA and HR-pQCT measurements were done in a median time of 7 [6–11] days after KTx (Table 2). Regarding DXA results, the median T-score was −1.4 [−2.3 – −0.2] at LS, −1.5 ± 0.98 at FN, and −1.2 ± 1.05 at TH. Twenty percent of patients had osteoporosis at LS, 16% at the FN, and 8% at TH (Table 2). The median TBS-V3 score was 1.316 [1.256 – 1.401] and 64.4% of the patients had a value below 1.370. The HR-pQCT parameters demonstrated a mean value of Tt vBMD of 257 ± 61.2 mg HA/cm^3 and 278 ± 62.9 mg HA/cm^3 at the tibia and radius sites, respectively. vBMD data, geometry, and structural parameters are detailed in Table 2.

We examined the association between TBS < 1.370 and clinical, biological, and bone microarchitecture parameters at baseline. Patients with TBS < 1.370 were significantly older (63.1 vs. 55.9 years; $p = 0.002$) and had a higher BMI (26.9 vs. 24.5 kg/m^2; $p = 0.03$). No other demographic or biological markers were significantly associated with the TBS cut-off. Patients with diabetic nephropathy as the leading cause of CKD did not have significantly lower TBS compared to those with non-diabetic CKD (1.285 ± 0.088 for diabetic CKD vs. 1.322 ± 0.119 for non-diabetic CKD; $p = 0.4$). At the time of KTx, no differences were observed in the proportion of patients with TBS < 1.370 or ≥ 1.370 based on the cause of CKD. Similarly, no significant differences in mean TBS values were observed across these groups. When stratified by the TBS cut-off of 1.370, no differences were found in the proportion of patients below

Table 2 Bone parameters evaluated by DXA and HR-pQCT ($n=75$)

DXA parameters		
	Lumbar Spine aBMD (g/cm^2)	0.908 [0.801 – 1.025]
	Lumbar Spine T-score	−1.4 [−2.3 – −0.2]
	Total Hip aBMD (g/cm^2)	0.839 ± 0.156
	Total Hip T-score	−1.2 ± 1.05
	Neck Hip aBMD (g/cm^2)	0.684 [0.59 – 0.758]
	Neck Hip T-score	−1.5 ± 0.98
	DXA TBS-V3	1.316 [1.256 – 1.401]
	DXA TBS-V4	1.305 [1.236 – 1.351]
HR-pQCT parameters	**Radius parameters**	**Tibia parameters**
Volumetric BMD (mg HA/cm^3)		
Total	278 ± 62.9$^{\$}$	257 ± 61.2
Trabecular	148 ± 43.8$^{\$}$	143.9 ± 44.1
Cortical	836 ± 60.2$^{\$}$	839 ± 69.7$^{\$}$
Geometry parameters (mm^2)		
Total Area	356.5 ± 115.0	781.4 ± 173.8
Cortical Perimeter	79.4 ± 11.9	109 ± 12.3
Cortical Area	65.3 ± 15.3	126.1 ± 30.9
Trabecular Area	295.5 ± 107.6	662 ± 166
Structural parameters		
BV/TV (%)	0.204 [0.174 – 0.261]	0.204 [0.166– 0.259]$^{\$}$
Tb.N (1/mm)	1.38 ± 0.27$^{\$}$	1.25 ± 0.28$^{\$}$
Tb.Th (mm)	0.232 ± 0.021	0.248 ± 0.025
Tb.Sp (mm)	0.693 [0.595 – 0.793]$^{\#}$	0.766 [0.689 – 0.910]$^{\#}$
Tb.1/N.SD (mm)	0.262 [0.222 – 0.319]$^{\#}$	0.324 [0.274 – 0.405]$^{\#}$
Ct.Th (mm)	0.980 ± 0.185	1.362 ± 0.322
Ct.Po (mm)	0.009 [0.005 – 0.014]	0.022 [0.015 – 0.037]
Ct.Po.Dm (mm)	0.190 ± 0.03	0.221 ± 0.04

Data are presented either as median [IQR] or mean ± SD depending on the distribution

$^{\$}$ Parameters statistically lower in case of TBS < 1.37 compared to TBS ≥ 1.37 ($p<0.03$)

$^{\#}$ Parameters statistically higher in case of TBS < 1.37 compared to TBS ≥ 1.37 ($p<0.03$)

aBMD areal bone mineral density, *BV/TV* trabecular bone volume fraction, *Ct.Th* cortical thickness, *Ct.Po* intra-cortical porosity, *Ct.Po.Dm* cortical pore diameter, *DXA* dual-energy X-ray absorptiometry, *HR-pQCT* high resolution peripheral computed tomography scan, *IQR* interquartile range; mg *HA/cm^3* milligrams of hydroxyapatite per cubic centimetre, *MOF* major osteoporotic fracture, *TBS* trabecular bone score, *Tb.N* trabecular number, *Tb.Th* trabecular thickness, *Tb.Sp* trabecular separation, *Tb.1/NSD* standard deviation of 1/Tb.N inhomogeneity of network *SD* standard deviation, *TBS-V4* version 4.0 of the TBS analysis

or above this threshold based on fracture or parathyroidectomy history. Additionally, no difference in aBMD at the three sites were observed in patients with low TBS.

When patients were stratified based on their TBS values (< 1.370 or ≥ 1.370), univariate and multivariate logistic regression analyses were performed with HR-pQCT parameters. We observed that patients with low TBS had significantly lower values of Tt, Tb, and Ct vBMD, as well as a lower trabecular bone volume fraction (BV/TV) and trabecular number (Tb.N). Moreover, they exhibited significantly higher levels of Tb.Sp and Tb 1/N.SD (Table 2&Table 3& Supplementary Table 1). In contrast, using T-score level, we did not find any differences in HR-pQCT parameters at radius site in patients above or below −2.5 T-score at LS or FN levels ($p>0.06$) (Supplementary Table 2).

In multivariate regression analysis, age (OR: 1.078; 95% CI: 1.019 – 1.140), BMI (OR: 1.176; 95% CI: 1.006 – 1.376), and Tb.N (OR: 0.018; 95% CI: 0.001 – 0.240) remained independently associated with a TBS below 1.370, indicating that older age, higher BMI, and reduced trabecular number significantly increase the likelihood of having a lower TBS. In multivariate analysis using a cut-off of −2.5 for the T-score at the LS aBMD, no demographic or structural HR-pQCT parameters were associated with a low aBMD (≤ −2.5).

When a lower TBS cut-off (< 1.310) was used, as previously associated with fracture risk [27], multivariate

Table 3 Demographic, biological and HR-pQCT parameters associated with TBS-V3 < 1.370 at time of kidney transplantation

Parameters	OR	95% confidence interval	*p*-value
Age (years)	1.082	1.03 – 1.138	0.002
BMI (kg/m^2)	1.137	1.011 – 1.279	0.03
R Tt vBMD	0.989	0.98 – 0.998	0.01
R Tb vBMD	0.987	0.976 – 0.999	0.03
R Ct vBMD	0.989	0.979 – 0.998	0.02
R BV/TV (log)	0.179	0 .033 – 0.988	0.048
R Tb.N	0.089	0.012 – 0.677	0.02
R Tb.Sp (log)	23.0	1.84 – 287.6	0.02
R Tb.1/N.SD (log)	20.5	2.38 – 176.4	0.006
T Ct vBMD	0.99	0.98 – 0.99	0.006
T Tb.N	0.08	0.01 – 0.6	0.03
T Tb.Sp (log)	27.13	2.12 – 348.05	0.01
T Tb.1/N.SD (log)	11.01	1.60 – 76.3	0.02

Univariate parameters have been selected if *p* values were < 0.05

BMI body mass index, *BV/TV* trabecular bone volume fraction, *Ct* cortical, *HR-pQCT* high resolution peripheral computed tomography scan, *Tt* Total, *Tb* trabecular, *Tb.N* trabecular number, *Tb.Sp* trabecular separation, *Tb.1/N.SD* standard deviation of 1/Tb.N: inhomogeneity of network, *T* tibia, *R* radius, *vBMD* volumetric bone mineral density

regression analysis identified age, female sex, and Tb.N as independent factors associated with lower TBS.

Correlations between TBS and HR-pQCT parameters are presented in Table 4. The correlations have been adjusted for age, BMI, and aBMD at the LS, as shown in Table 4. In univariate analysis, there was a significant correlation between TBS and vBMD parameters. TBS significantly correlated with Tt, Tb and Ct vBMD (r between 0.242 and 0.389; $p < 0.03$) and trabecular numbers (Tb.N (r between 0.330 and 0.360; $p < 0.006$)). A negative correlation was observed between TBS and the trabecular separation (Tb.Sp) and inhomogeneity of network (Tb 1/N.SD) (r between −0.368 and −0.445; $p < 0.002$), but also with the cortical structure at both sites (cortical porosity (Ct.Po) and diameter of cortical pores (Ct.Po.Dm) (r between −0.250 and −0.295; $p < 0.03$).

In Supplementary Table 3 we present the correlation between HR-pQCT and aBMD at the three sites. aBMD results were also correlated with vBMD parameters (Tt, Tb and Ct vBMD (r between 0.240 and 0.545; $p < 0.03$) and Tb.N and BV/TV (r between 0.430 and 0.794; $p < 0.001$). A negative correlation was observed between aBMD and Tb.Sp, Tb.1/N.SD and cortical thickness (Ct.Th) (r between −0.299 and −0.721; $p < 0.009$)). However, unlike TBS, aBMD was not correlated with cortical porosity parameters.

In the sensitivity analysis the median TBS-V4 was 1.305 [1.236 – 1.351] and the ICC between software versions was 0.80 (95% CI: 0.73 – 0.87), and is therefore significant. Seventy eight percent of patients had a value below 1.370 using the TBS-V4. The sensitivity analysis using the TBS-V4 demonstrated a negative correlation with age ($r = -0.278$; $p = 0.02$), and no other demographic or biological correlations were observed. TBS-V4 showed a correlation with aBMD at LS ($r = 0.511$; $p < 0.0001$), TH ($r = 0.452$; $p = 0.0001$), and FN ($r = 0.377$; $p = 0.001$). Using the TBS-V4, univariate regression analyses revealed that a lower TBS (below 1.370) was not associated with clinical or biological parameters but was linked exclusively to volumetric and structural parameters measured by HR-pQCT. In multivariate regression analysis, Ct vBMD (OR: 0.987; 95% CI: 0.974 – 0.999) was independently associated with low TBS, indicating that reduced cortical density increases the likelihood of having a lower TBS using de pre-market software version 4. Finally, when applying the lower TBS cut-off (< 1.310), Tb.N became independently associated with the likelihood of low TBS (OR: 0.051; 95% CI: 0.005 – 0.054; $p = 0.01$). In Supplementary Table 4 & 5, we present the correlation between HR-pQCT and the TBS-V4 values, which are consistent with those initially obtained using the TBS-V3 version. However, the correlation with vBMD parameters and trabecular structures appeared to be stronger, while the previously observed correlations with cortical structural (Ct.Po and Ct.Po.Dm) parameters were no longer observed.

Discussion

In this cross-sectional analysis, we investigated the potential role of TBS in assessing bone microarchitecture in patients with ESRD. Our results showed that patients with low TBS exhibited significantly lower Tt, Tb, and Ct vBMD, along with reduced BV/TV and Tb.N, while displaying increased Tb.Sp. In contrast, T-score-based classification did not distinguish differences in HR-pQCT parameters. Multivariate regression analysis identified older age, higher BMI, and lower Tb.N as independent predictors of low TBS, whereas no HR-pQCT parameters were associated with low aBMD (T-score ≤ −2.5). Moreover, the negative correlation observed between TBS and Ct.Po at both sites with HR-pQCT might reflect the trabecularization of the endocortical bone observed in histomorphometry analysis in CKD patients [3, 30]. This non-invasive technique could thus help capturing bone fragility parameters that are important determinants of fracture risk, which is not captured by bone density alone.

Similar correlations have been demonstrated within the general population between TBS and both vBMD and the microarchitecture of the trabecular and cortical compartments in HR-pQCT analyses [31]. However, the associations between TBS and HR-pQCT in ESRD patients have been poorly studied. Luckman et al. conducted a post hoc analysis

Table 4 TBS correlations with HR-pQCT parameters ($n=73$)

HR-pQCT parameters	Tt.vBMD	Tb.vBMD	Ct.vBMD	BV/TV	Tb.N	Tb.Th	Tb.Sp	Tb.1/N.SD	Ct.Th	Ct.Po	Ct.Po.Dm
Radius											
TBS-V3	0.370 (**0.001**)	0.300 (**0.01**)	0.347 (**0.003**)	0.271 (**0.02**)	0.335 (**0.004**)	−0.049 (0.7)	−0.368 (**0.001**)	−0.445 (**0.0001**)	0.200 (0.09)	−0.281 (**0.02**)	−0.249 (**0.03**)
TBS-V3 adjusted1	0.417 (**0.002**)	0.384 (**0.008**)	0.393 (**0.006**)	0.345 (**0.003**)	0.418 (**0.002**)	0.060 (0.6)	−0.431 (**0.0001**)	−0.469 (**< 0.0001**)	0.356 (**0.002**)	−0.114 (0.3)	−0.113 (0.3)
TBS-V3 adjusted2	0.292 (**0.01**)	0.210 (0.07)	0.315 (**0.007**)	0.169 (0.2)	0.271 (**0.02**)	−0.092 (0.4)	−0.285 (**0.01**)	−0.354 (**0.002**)	0.236 (**0.04**)	−0.130 (0.3)	−0.131 (0.3)
Tibia											
TBS-V3	0.242 (**0.04**)	0.212 (0.07)	0.388 (**0.0007**)	0.167 (0.2)	0.360 (**0.002**)	−0.058 (0.6)	−0.379 (**0.001**)	−0.424 (**0.0002**)	0.131 (0.3)	−0.253 (**0.03**)	−0.061 (0.6)
TBS-V3 adjusted1	0.331 (**0.04**)	0.391 (**0.0006**)	0.292 (**0.01**)	0.341 (**0.003**)	0.497 (**< 0.0001**)	0.125 (0.3)	−0.494 (**< 0.0001**)	−0.413 (**0.0003**)	0.251 (**0.03**)	−0.100 (0.4)	−0.010 (0.9)
TBS-V3 adjusted2	0.178 (0.1)	0.203 (0.08)	0.194 (0.1)	0.158 (0.2)	0.336 (**0.004**)	0.031 (0.8)	−0.346 (**0.003**)	−0.313 (**0.0071**)	0.142 (0.2)	−0.06 (0.6)	−0.045 (0.7)

Data are presented as correlation coefficients (r) and their corresponding *p*-values (*p*-value)

Significant correlations are in bold

TBS-V3 adjusted1: TBS-V3 variable adjusted for age and body mass index

TBS-V3 adjusted2: TBS-V3 variable adjusted for age, body mass index and aBMD at LS

aBMD areal bone mineral density, *BV/TV* trabecular bone volume fraction, *Ct* cortical, *Ct.Th* cortical thickness, *Ct.Po* intra-cortical porosity, *Ct.Po.dm* cortical pore diameter, *HR-pQCT* high resolution peripheral computed tomography scan, *LS* lumbar spine, *TBS* trabecular bone score, *Tt* Total, *Tb* trabecular, *Tb.N* trabecular number, *Tb.Th* trabecular thickness, *Tb.Sp* trabecular separation, *Tb.1/NSD* standard deviation of 1/Tb.N inhomogeneity of network, *vBMD* volumetric bone mineral density

in a small cohort of 47 KTRs [32], considering TBS and HR-pQCT parameters measured at 3 months post-KTx. In their study, less than 50% of patients were on dialysis before KTx, and no fractures prior to KTx were noted. All patients had normal T-scores at all sites, yet 42% of those with normal BMD were classified as high fracture risk based on TBS values below 1.370. In the Luckman et al. study, negative correlations were observed between TBS and trabecular structure at the radius site (Tb.Sp and Tb 1/N.SD), and with cortical structure (Ct.Po) at the tibia site. We demonstrate the same significant negative correlations between TBS and trabecular and cortical parameters but at both radius and tibia sites. Our results compared to Luckman et al. [32] might be more generalizable due to the characteristics of the population included, and the shorter timing of imaging analysis performed after KTx (median of 7 [6–11] days post-KTx). This difference in timing could have influenced the findings, as significant changes in bone parameters can occur within the first few months post-KTx, as demonstrated by Chandran et al. [33].

Ramalho et al. [34] studied the correlation between TBS and HR-pQCT parameters in 50 CKD patients at different stages of CKD (stages 2 to 5D). In their study, HR-pQCT parameters at the radius site (Tt and Tb vBMD, as well as BV/TV, Tb.N, Tb.Th, and Tb.Sp) were correlated with TBS. At the tibia site, other parameters (Tt and Ct vBMD, as well as Ct.Th) were correlated with TBS. The analyses in Ramalho's study were performed with different machines at two different sites, and only two-thirds of the patients were on dialysis at the time of analysis. Our results confirm the data of Ramalho with a more generalizable population and provide more reliable data at both sites.

The TBS was initially developed and validated to reflect trabecular changes [29]. Previous data have demonstrated that TBS can indicate trabecular changes at the radius site and cortical changes at the tibia site in CKD patients [32, 34]. Our findings show that the impact of global mineral changes observed in CKD significantly could affects both the cortical and the trabecular compartment at both sites as in the general population [31]. However, as observed in the general population, the risk prediction of trabecular changes at the radius site is higher [17]. More parameters measured at the distal radius significantly predict both incident fractures and MOFs compared to those measured at the distal tibia. Therefore, the distal radius is a more preferable site for fracture prediction [35]. The distal radius of the non-dominant side, being a non-weight-bearing region, provides a sensitive site for osteoporosis detection, as osteoporosis developed here is not offset by most osteogenic weight-bearing activities. In contrast, the distal tibia, as a weight-bearing site, is influenced by daily activities and cannot predict fragility fractures as effectively as the distal radius [17].

In our cohort, no significant correlation was found between TBS and aBMD parameters, except for a weak correlation with TH aBMD ($r = 0.283$, $p = 0.015$). TBS likely as a better correlation with cortical bone structure demonstrated by histomorphometry study [34], explaining the correlation observed with TH in our cohort. In the study by Luckman et al. [32], correlations were observed between TBS and aBMD, particularly at the LS site ($r = 0.5$), but all their patients had normal BMD. This discrepancy might also be explained by the impact of degenerative changes (e.g., scoliosis) that could falsely increase aBMD readings without affecting TBS [36, 37].

The cut-off value of 1.370 for TBS, associated with a higher risk of fracture, has not been validated in large studies. Naylor et al. investigated TBS in 327 adults three months after KTx and found a significantly lower TBS compared to controls [26]. Fracture sustainers had a notably lower TBS than non-sustainers ($p = 0.003$), with a cut-off TBS value below 1.370. Those with lower TBS were less likely to remain fracture-free ($p = 0.017$) [26]. Aleksova et al. [27] studied TBS in 147 ESRD patients who underwent KTx. The mean TBS value was 1.345 ± 0.125. In this cohort, prevalent non-vertebral fractures were significantly associated with lower TBS values ($p = 0.023$) after transplantation. Low TBS values were a good predictor of non-vertebral fractures. In our cohort, a cut-off value of 1.370 was able to differentiate patients with a lower level of vBMD observed by HR-pQCT, but not those with an aBMD level of −2.5 at the LS level (Supplementary Table 1 & 2). Future longitudinal studies are needed to confirm the threshold for TBS and to investigate whether changes in TBS are influenced by treatment and ultimately impact fracture risk [26].

Using the version of the TBS software, we demonstrated that mean TBS-V4 values were significantly lower than TBS-V3 values ($p = 0.02$), with a significant agreement between the two versions (ICC was 0.80). We observed a stronger correlation between the TBS-V4 values and both HR-pQCT parameters (especially trabecular structure) and aBMD at major sites (Supplementary Table 4 & 5). There will be small differences between the TBS-V3 derived locally with a calibration, and the pre-market TBS-V4 values derived by Medimaps without calibration. However, these small offsets will be very minor and will not impact correlation analyses. However, the results of the multivariate analysis identify cortical density independently associated with lower TBS values when using the TBS-V4. These findings suggest that the TBS-V4 may require the establishment of a new cut-off value to better reflect long-term fracture risk in KTx patients. Furthermore, the improved algorithm, which adjusts for directly measured abdominal soft tissue

thickness, strengthened the correlation with trabecular structure but was less predictive of changes in cortical structure.

In our study, we did not demonstrate a correlation between the values of different biomarkers and TBS, as also shown in another study [38]. In contrast, Aleksova's study showed an inverse correlation between PTH and P1NP values and TBS [27]. These correlations could be explained by the very high levels of these two biomarkers observed in this study at the time of KTx compared to ours. Improving the management of mineral disorders observed in ESRD patients is paramount and could therefore improve microarchitectural abnormalities. Moreover, only C-telopeptides values were shown to be correlated with low TBS in Luckman's study, with no correlation between PTH and TBS observed [32]. Analyzing C-telopeptides in patients with CKD remains challenging due to the renal clearance of C-telopeptides and the difficulty of analyzing these parameters in ESRD patients.

Other limitations of the study include the relatively small sample size; however, our cohort of 75 patients is one of the largest published to date. Additionally, histomorphometry data are lacking [34]. Another limitation is the cross-sectional design of the study, which allows only for the description of associations, but not causality. Moreover, the discriminatory power of HR-pQCT data in assessing fracture risk is still uncertain [18]. Future studies should include longitudinal follow-up and the incorporation of HR-pQCT parameters alongside biomarkers of bone turnover and histomorphometry data to improve fracture risk prediction and assessment after KTx.

In conclusion, our findings suggest that TBS has the potential to be an accessible tool for evaluating and monitoring bone quality and strength in CKD patients. TBS was correlated with trabecular bone, similarly to aBMD, but, unlike aBMD, TBS was also associated with cortical bone parameters measured by HR-pQCT. Further longitudinal studies are needed to confirm the role of TBS as a diagnostic tool for predicting fractures in CKD patients, and to compare it with histomorphometry data.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11657-025-01519-2.

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Data Availability The data used in this study can be provided upon request if needed.

Declarations

Conflict of interest BOUQUEGNEAU Antoine, JOURET François, SEIDEL Laurence, BONVOISIN Catherine, WEEKERS Laurent, BRUYERE Olivier, RIBBENS Clio, and MALAISE Olivier declare that they have no conflict of interest.
CAVALIER Etienne is a consultant for IDS, DiaSorin, Nittobo, Fujirebio, Roche Diagnostics, and SNIBE.
DELANAYE Pierre is a consultant for IDS.

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