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Trabecular Bone Score Improves Early After Successful Kidney Transplantation Irrespective of Antiresorptive Therapy and Changes in Bone Mineral Density

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Background. Trabecular bone score (TBS) is a new tool to assess trabecular bone microarchitecture based on standard dual-energy x-ray absorptiometry (DXA) of lumbar spine images. TBS may be important to assess bone quality and fracture susceptibility in kidney transplant recipients (KTRs). This study aimed to investigate the effect of different bone therapies on TBS in KTRs. **Methods.** We reanalyzed DXA scans to assess TBS in 121 de novo KTRs at baseline, 10 wk, and 1 y. This cohort, between 2007 and 2009, participated in a randomized, placebo-controlled trial evaluating the effect of ibandronate versus placebo in addition to vitamin D and calcium. **Results.** Although bone mineral density (BMD) Z scores showed a subtle decrease in the first weeks, TBS Z scores increased from baseline to 10 wk for both treatment groups, followed by a slight decline at 12 mo. When comparing treatment groups and adjusting for baseline TBS, there were no differences found in TBS at 12 mo ($P = 0.419$). Correlation between TBS and BMD at baseline was weak (Spearman's $\rho = 0.234$, $P = 0.010$), and change in TBS was not correlated with changes in lumbar spine BMD in either of the groups ($\rho = 0.003$, $P = 0.973$). **Conclusions.** Treatment with ibandronate or vitamin D and calcium did not affect bone quality as measured by TBS in de novo KTRs, but TBS increased early, irrespective of intervention. Changes in TBS and BMD during the study period were not correlated, indicating that these measurements reflect different aspects of bone integrity. TBS may complement BMD assessment in identifying KTRs with a high fracture risk.

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Patients with chronic kidney disease (CKD) have impaired bone mineral density (BMD) and bone quality and are at increased risk of fractures compared with the general population.[1] Patients with CKD also have greater postfracture morbidity and mortality.[2] In kidney transplant recipients (KTRs), additional risk factors, such as initial high dose of glucocorticoids, are added to the effect of long-standing uremia, further threatening bone integrity. Early studies demonstrated significant loss of BMD in KTRs compared with patients with CKD[3] and a higher fracture prevalence than patients undergoing dialysis.[4] Despite modern immunosuppressive regimens being more gentle in their effect on bone tissue,[5,6] many KTRs with high fracture risk go undetected, and standalone imaging techniques do not seem to predict fracture rates in this vulnerable patient group.[7]

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Trabecular bone score (TBS) is a software-based calculation to assess trabecular bone microarchitecture, or bone quality, based on standard dual-energy x-ray absorptiometry (DXA) of lumbar spine images.[8] TBS is a useful measure for fracture risk prediction in patients with normal and reduced kidney function, independent of BMD, age, sex, and the fracture risk assessment tool (FRAX) score.[9-13] As has been demonstrated in patients with CKD on hemodialysis,[14] KTRs have generally lower TBS than the background population.[10,15,16] However, studies on the effect of common antifracture therapies on TBS in KTRs are scarce.[16]

In our double-blind, randomized, placebo-controlled trial investigating early bisphosphonate treatment in KTRs,[17] the primary outcome, relative change in lumbar spine BMD, did not improve significantly with 12 mo of ibandronate in addition to vitamin D and calcium. However, the study demonstrated lowering of biochemical markers of bone turnover and improvement in BMD, both in the total femur region and ultradistal radius, in patients on ibandronate (secondary endpoints).

In this post hoc analysis of the above-mentioned trial, we examined the effect of ibandronate, vitamin D, and calcium on TBS. Our hypothesis was that antiresorptive therapy with ibandronate would positively affect TBS after kidney transplantation. Although we assumed that development in TBS and BMD would be correlated, we postulated TBS to be a more sensitive marker of treatment effect than BMD.

MATERIAL AND METHODS

Study Population

Patient selection criteria, treatment interventions, and baseline characteristics of the clinical trial cohort have been described in detail previously.[17] In short, 129 KTRs transplanted between January 2007 and December 2009 were included in a 1-y prospective, randomized, placebo-controlled trial. Patients with an adequate graft function (estimated glomerular filtration rate of at least 30 mL/min/1.73 m^2) who were clinically stable during 7 consecutive days had baseline study investigations performed within 5 wk after transplantation. Eligible patients were randomly assigned in 1:1 to treatment with either intravenous ibandronate 3 mg or placebo (intravenous isotonic saline) every 3 mo for 1 y. All patients received supplementation of calcium (1 g/d) and active vitamin D_3 (0.25 μg/d). At the time of conducting the randomized controlled trial (RCT), many transplant centers recommended vitamin D and calcium for all de novo KTRs. Thus, when planning the RCT, we decided that all patients should receive vitamin D and calcium as basic preventative therapy to assure international (external) validity. Main exclusion criteria were hypercalcemia, treatment for bone disease within the previous 12 mo, and parathyroidectomy. Routinely, DXA scans were performed at 8 to 10 wk and 12 mo. Because of the RCT, 2 DXA scans were performed within a short time interval, both at baseline (within 5 wk) and 10 wk, before discharge to a local hospital. Of the trial participants, 121 patients had valid DXA scans at baseline, 10 wk, and 12 mo, available for TBS assessment in the lumbar spine.

Demographic Information

Background information, data on comorbidities, and laboratory data of the trial participants were systematically collected at baseline.

Immunosuppressive Therapy

The standard immunosuppressive protocol consisted of induction with basiliximab and methylprednisolone followed by maintenance therapy including a low-dose calcineurin inhibitor (cyclosporine or tacrolimus), prednisolone, and mycophenolate, as described previously.[17]

DXA Measurements

For the DXA measurements, we used a narrow fan-beam GE Lunar Prodigy densitometer (GE Medical Systems, Lunar Corp., Madison, WI). DXA scans were measured at baseline (on average 16 d after transplantation), 10 wk, and 12 mo after transplantation. No hardware changes were made during the study period, but there were several upgrades of the software during the study time. All the scans were reanalyzed in February 2023 by the same software version 18 (SP3; GE Medical Systems, Lunar Corp., Madison, WI).[18]

We analyzed anterior–posterior lumbar spine (L1–L4) and presented BMD for this region. Further details on calculating BMD lumbar spine have been described previously.[19] Absolute BMD values (g/cm^2) and Z scores were estimated by comparison with the reference population in the software, suitable for clinical use in a Norwegian population.[20] Daily calibration was performed.[21] The short- and long-term coefficients of variation for our densitometer were 0.8% and 1.4%, respectively.[22]

Assessment of TBS

Lumbar spine TBS parameters were retrospectively analyzed from DXA L1 to L4 images by using TBS iNsight software (version 3.0.3.0; Medimaps Group, Geneva, Switzerland). One of the investigators (K.G., an International Society for Clinical Densitometry–certified densitometry technologist) performed all the analyses based on the original scans. Compressed vertebras were excluded from the analyses. TBS measurements in patients with body mass index ≥37 kg/m^2 (n = 2) were included in the analysis but were not validated by the software. Absolute TBS values were analyzed in all study subjects, but TBS for age and gender (TBS Z score) was provided by the manufacture (TBS iNsight) reference database and was only available for women aged 45 y and older and men aged 40 y and older (n = 92).

We calculated Z scores for BMD and TBS to compare with normative data.

Statistics

Statistical analyses were performed using SPSS for Windows, version 28 (SPSS, Chicago, IL). For continuous parameters, we compared the RCT participants using the independent sample *t* test or Mann-Whitney *U* test, depending on the distribution of data. Categorical variables were analyzed using the chi-square test. Within-group changes in BMD and TBS during the study period were analyzed using the paired *t* test. We performed a 1-sample *t* test for Z scores on each group with 0 as the hypothesized mean. We used ANCOVA with adjustment for baseline TBS values to evaluate the potential effects of calcium and vitamin D with/without concomitant ibandronate on TBS 12 mo after transplantation. We investigated Spearman's correlations between baseline TBS and lumbar spine BMD and changes in TBS and BMD during the study duration. A *P* value of 0.05 was chosen as a cutoff for statistical significance, and all reported *P* values were 2-tailed.

Ethics

The study was approved by the Regional Ethics Committee for Medical Research in Southern Norway, the Norwegian Directorate of Health, the Norwegian Data Inspectorate, and the Norwegian Medicines Control Agency. The trial was registered at www.clinicaltrials.gov as NCT00423384 and with EudraCT number 2006-003884-30. The current study was conducted in compliance with the Declaration of Helsinki-II. All patients gave written informed consent for trial participation.

RESULTS

Baseline

Baseline demographics and characteristics of the study population are presented in Table 1. TBS was lower in both groups compared with normative data (Z scores). Diabetes was more prevalent in the placebo group of the RCT (25% versus 9% in the ibandronate group), whereas other characteristics were similar between the 2 groups. Baseline serum creatinine and mineral metabolism markers were comparable; the longitudinal changes throughout the study can be seen in **Table S1** (**SDC,** http://links.lww.com/TXD/A601).

TBS and BMD

Figures 1 and 2 show the development in Z scores for both TBS and BMD over time. TBS showed an increase from baseline to 10 wk, irrespective of treatment, with mean Z score values improving in the ibandronate group +0.28 (SD 0.80) and placebo (vitamin D/calcium group) +0.42 (SD 0.83). This early positive development in TBS was followed by a slight decline (data not shown) to 1 y after transplantation. The time-trend was the same in a sensitivity analysis using absolute TBS values, including all RCT patients (n = 129). There was a uniform trend that BMD in the lumbar spine showed some deterioration in the first posttransplant weeks to improve during the upcoming study period.

Changes in absolute values of TBS and BMD from baseline to 12 mo after transplantation are described in Table 2. Mean TBS increased in all groups. With adjustments for baseline values in the ANCOVA analyses, we found no significant group differences for TBS at 12 mo ($P = 0.419$). BMD increased in the ibandronate group during the study duration (+1.7%, SD 5.5). There were, however, no significant group differences in BMD at the study end when adjusting for baseline values ($P = 0.083$).

In total, only 3 patients (1 receiving ibandronate and 2 in the placebo group) had baseline BMD T scores of <–2.5, making analyses of treatment effect futile for this subgroup. However, Tables 3 and 4 present the development in TBS and BMD for the 2 groups stratified by baseline L1 to L4 BMD T score of <–1 and ≥–1 as a cutoff, respectively. Like in the overall analysis, no clear treatment effect on TBS could be detected in the stratified analyses; however, lumbar spine

TABLE 1.

Demographics and baseline characteristics

Variable	Ibandronate/VitD/Ca (N = 62)	Placebo/VitD/Ca (N = 59)	*P*
Age, y, mean (SD)	49.6 (14.7)	51.5 (12.8)	0.452
Gender, male	48 (76)	46 (78)	0.942
Ethnicity, Caucasian	60 (96.8)	59 (100)	0.164
BMI, kg/m^2, mean (SD)	25.5 (3.5)	25.1 (3.6)	0.532
Current or previous smoking	40 (65)	40 (68)	0.703
Previous kidney transplant	10 (15.9)	8 (13.6)	0.880
Time since start of KRT, mo, median (IQR)	10 (25)	9 (19)	0.961
Pre-Tx diabetes	6 (9.2)	15 (25.4)	0.022
Diabetes as cause of kidney failure	2 (3.2)	11 (18.6)	0.006
Immunological cause of kidney failure	29 (46.7)	22 (37.3)	0.291
CNI, tacrolimus	32 (50.8)	25 (42.4)	0.309
BMD L1–L4, g/cm^2, mean (SD)	1.168 (0.177)	1.198 (0.146)	0.568
BMD Z score, mean (SD)	–0.38 (1.407)	–0.14 (1.161)	0.307
TBS L1–L4, mean (SD)	1.249 (0.138)	1.265 (0.162)	0.486
TBS Z score, mean (SD; n = 92)	–1.12 (1.354)	–1.12 (1.596)	0.998
P-creatinine, µmol/L, mean (SD)	110.0 (24.9)	113.8 (26.5)	0.414
P-calcium, mmol/L, mean (SD)	2.32 (0.13)	2.35 (0.12)	0.176
P-phosphate, mmol/L, mean (SD)	0.69 (0.22)	0.72 (0.18)	0.465
P-PTH, pmol/L, median (IQR)	12.3 (12.2)	12.0 (8.9)	0.924
P-25-OH-VitD, nmol/L, mean (SD)	60.9 (23.0)	61.2 (32.2)	0.951

Number (%) unless otherwise stated. Data expressed as mean (SD) for normally distributed data and median (IQR) for nonnormal distributions. Categorical data expressed as absolute numbers with frequencies. *P* values for comparisons between RCT participants, *t* test, Mann-Whitney *U* test, and chi-square test as seen appropriate.

BMD, bone mineral density; BMI, body mass index; CNI, calcineurin inhibitor; IQR, interquartile range; KRT, kidney replacement therapy; P, plasma; Pre-Tx, pretransplant; PTH, parathyroid hormone; RCT, randomized controlled trial; TBS, trabecular bone score; 25-OH-VitD, 25 hydroxy vitamin D.

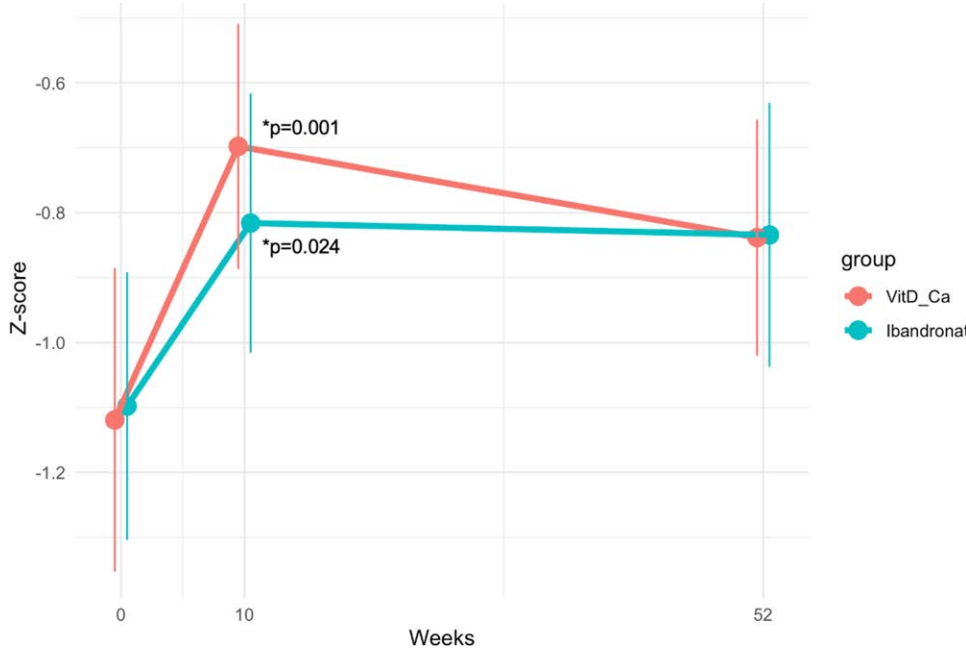

FIGURE 1. TBS L1–L4 Z score at baseline, 10 wk, and 12 mo, data presented as mean (±SEM); *representing significant changes from baseline ($P < 0.05$). TBS, trabecular bone score.

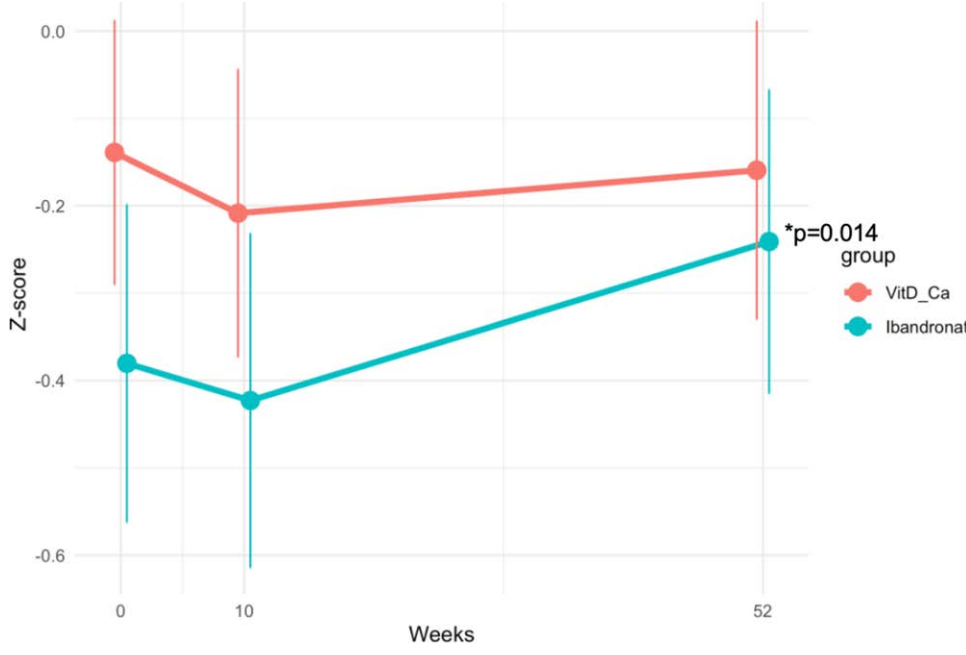

FIGURE 2. BMD L1–L4 Z score at baseline, 10 wk, and 12 mo, data presented as mean (±SEM); *representing significant changes from baseline ($P < 0.05$). BMD, bone mineral density.

BMD increased significantly in the osteopenic group after ibandronate treatment.

The correlation between TBS and BMD at baseline was weak (Spearman' $\rho = 0.234$, $P = 0.010$). In a pooled analysis of all patients, change in TBS was not correlated with change in lumbar spine BMD ($\rho = 0.003$, $P = 0.973$; Figure 3).

DISCUSSION

In this study of de novo KTRs, the TBS Z score improved within weeks after the restoration of kidney function despite no gain in BMD in the early period. Treatment with ibandronate in addition to vitamin D and calcium in the first year after transplantation did not offer any benefit for TBS compared with vitamin D and calcium alone. Changes in TBS during the first posttransplant year showed a weak, nonsignificant correlation with changes in BMD.

A cross-sectional study of 39 KTRs found that TBS recovered almost completely >10 y posttransplantation.[23] However, in apparent contrast to our results, a decline in TBS was seen from pretransplant to 12 mo after engraftment in a study of 11 KTRs looking specifically at different measures of bone

TABLE 2.

Lumbar spine BMD and TBS values at baseline vs study end; group differences analyzed by ANCOVA with adjustment for baseline values

	Ibandronate/ VitD/Ca (N = 62)	Placebo/VitD/Ca (N = 59)	ANCOVA
TBS			
Baseline, mean (SD)	1.230 (0.140)	1.250 (0.169)	$P = 0.419$
12 mo, mean (SD)	1.251 (0.139)	1.279 (0.152)	
Δ rel %, mean (SD)	+ 2.1 (9.5)	+ 3.1 (10.5)	
	$P = 0.125$	$P = 0.059$	
BMD			
Baseline, mean (SD)	1.142 (0.170)	1.159 (0.142)	$P = 0.083$
12 mo, mean (SD)	1.159 (0.165)	1.156 (0.165)	
Δ rel %, mean (SD)	+1.7 (5.5)	–0.3 (5.3)	
	$P = 0.031$	$P = 0.754$	

Data expressed as mean (SD). Paired *t* test *P* values for within-group differences; *P* values for ANCOVA representing overall between-group differences.
ANCOVA, analysis of covariance; BMD, bone mineral density; TBS, trabecular bone score; VitD, vitamin D.

TABLE 3.

Subgroup analyses, stratification by BMD at baseline: baseline L1–L4 BMD T score <–1 (osteopenia)

	Ibandronate/ VitD/Ca (N = 22)	Placebo/VitD/Ca (N = 10)	ANCOVA
TBS			
Baseline, mean (SD)	1.146 (0.141)	1.290 (0.133)	
12 mo, mean (SD)	1.193 (0.153)	1.310 (0.175)	$P = 0.881$
Δ rel %, mean (SD)	4.7 (12.0)	1.5 (7.8)	
	$P = 0.065$	$P = 0.540$	
BMD			
Baseline, mean (SD)	0.961 (0.058)	0.976 (0.110)	
12 mo, mean (SD)	0.987 (0.067)	0.967 (0.137)	$P = 0.130$
Δ rel %, mean (SD)	2.8 (5.7)	–1.1 (6.5)	
	$P = 0.036$	$P = 0.663$	

Data expressed as mean (SD). Paired *t* test *P* values for within-group differences; *P* values for ANCOVA representing between-group differences.
ANCOVA, analysis of covariance; BMD, bone mineral density; TBS, trabecular bone score; VitD, vitamin D.

TABLE 4.

Subgroup analyses, stratification by BMD at baseline: baseline L1–L4 BMD T score ≥–1 (normal BMD)

	Ibandronate/ VitD/Ca (N = 40)	Placebo/VitD/Ca (N = 49)	ANCOVA
TBS			
Baseline, mean (SD)	1.276 (0.117)	1.242 (0.175)	
12 mo, mean (SD)	1.283 (0.120)	1.273 (0.148)	$P = 0.551$
Δ rel %, mean (SD)	0.7 (7.7)	3.5 (11.0)	
	$P = 0.698$	$P = 0.078$	
BMD			
Baseline, mean (SD)	1.242 (0.121)	1.196 (0.118)	
12 mo, mean (SD)	1.254 (0.118)	1.195 (0.142)	$P = 0.291$
Δ rel %, mean (SD)	1.2 (5.3)	0.2 (5.1)	
	$P = 0.237$	$P = 0.890$	

Data expressed as mean (SD). Paired *t* test *P* values for within-group differences; *P* values for ANCOVA representing between-group differences.
ANCOVA, analysis of covariance; BMD, bone mineral density; TBS, trabecular bone score; VitD, vitamin D.

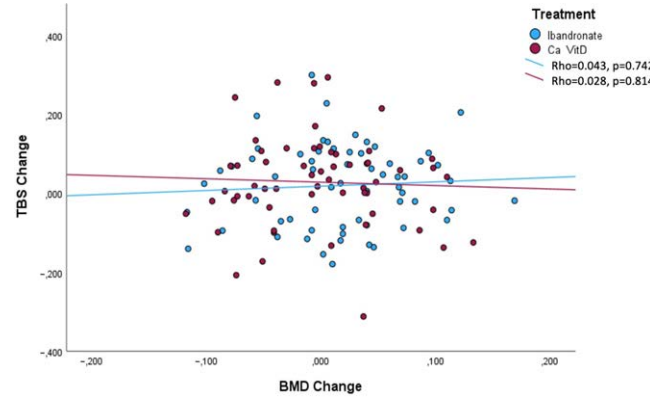

FIGURE 3. Spearman's ρ correlation between change in TBS and change in lumbar spine BMD (0–12 mo). The straight lines corresponding to the slope of a linear regression analysis. BMD, bone mineral density; TBS, trabecular bone score.

microarchitecture[24] and from shortly after transplantation to 6 mo later in a cohort of 164 Asian KTRs.[25] As the timing of baseline measurements varies somewhat between these studies, results are not directly comparable; however, we noted that our cohort presented with the poorest bone microarchitecture at baseline. In a previous study of marine n-3 polyunsaturated fatty acid in 132 de novo KTRs in our transplant center, there was no change in TBS from 8 wk to 12 mo after transplantation, irrespective of treatment protocol, but subgroup analyses were not performed.[26]

The first year after transplantation is unpredictable, where initial high doses of glucocorticoids inhibit osteoblasts, with a secondary increase in bone resorption.[6,27] Meanwhile, kidney function improves and parathyroid hormone decreases gradually in most patients, potentially slowing down an excessive bone turnover.[27,28] Our findings of a relatively well-maintained and stable BMD over time and an early improvement in TBS may reflect the better treatment of CKD-mineral and bone disorder (CKD-MBD) in late CKD stages, in addition to modern immunosuppressive protocols being associated with less loss of bone mass after kidney transplantation, as compared with previous protocols.[3,5,7,17,29]

However, it should be noted that the central research question in the original study was whether bisphosphonate treatment in the first posttransplant year could be an efficient strategy to reduce early bone loss in the general kidney transplant recipient. Patients who were already started on antiresorptive therapy for osteoporosis were excluded from participation; hence, our study results may not be representative of KTRs with severely deranged bone metabolism. Our RCT included patients with a reasonably well-maintained bone mass at baseline, of whom only 3 of 121 patients had an L1 to L4 BMD T score of ≤–2.5.

There are many benefits to measuring TBS in addition to BMD. It is more pertinent to assess bone fragility and fracture susceptibility for CKD and posttransplant patients than BMD T scores.[30] CKD-MBD patients can have normal bone

mass but qualitative deterioration in bone quality.[31] BMD is merely a quantitative measure with potential artifacts and limitations, especially in patients with CKD.[32] Conversely, TBS describes specifically bone microarchitecture.[8,33] BMD by DXA may underestimate true fracture risk for patients with CKD-MBD,[7] wherefores better tools for bone health assessments are warranted.[31] TBS is independent of lumbar spine and femoral neck BMD and FRAX estimation,[10,34] as such TBS seems to predict fractures for background population and KTRs.[10,12] Moreover, TBS is not affected by degenerative changes, such as BMD.[35,36] Furthermore, TBS is noninvasive, readily available, and inexpensive. Thus, we advocate that TBS is complementary to the classical BMD assessment.

Of great concern is that although our median BMD T score values are normal, the median value of TBS falls to <1.37, a cutoff value that has been used to identify KTRs at high fracture risk.[10] We have shown TBS to increase uniformly after recovery from the uremic state, but this happened irrespective of bone protective therapy. Even in subgroup analyses of patients with baseline BMD L1 to L4 T score of <–1, there was no clear treatment effect on TBS. Based on these findings, it seems reasonable to conclude that a one-size-fits-all treatment protocol with bisphosphonates to improve bone microarchitecture after kidney transplantation is not justified, but an individualized approach is necessary.

We found no correlation between changes in TBS and BMD during the study period and only a very weak correlation between baseline levels, indicating that these measurements reflect different aspects of bone integrity and metabolism. This is in accordance with a cross-sectional study of 39 KTRs with a 10-y follow-up.[23] Lack of correlation between TBS and BMD was also seen in other patient groups, such as acromegaly.[19] Moreover, no correlation between TBS and BMD could be demonstrated in de novo liver transplant patients with low bone mass, randomized to risedronate versus placebo in addition to calcium and vitamin D.[37]

In contrast to our results, a study investigating the effect of denosumab on TBS in 44 de novo KTRs found treatment with denosumab to improve TBS and have beneficial effect on BMD.[16] A moderate-to-strong correlation was observed between TBS and lumbar spine BMD, Spearman's ρ at 3 different time points ($\rho = 0.56–0.61$, $P < 0.001$).[16] Although bisphosphosphonate and denosumab are both regarded as antiresorptive treatments, they have different modes of action, and no head-to-head comparisons have been performed in KTRs. It is, therefore, difficult to compare bisphosphonate and denosumab treatment effects on TBS.

The reason for the lack of correlation between TBS and BMD in this larger study of KTRs is uncertain. Diabetes is associated with lower TBS and higher rates of fractures, even if BMD is maintained.[38,39] Hence, differences in the proportion of patients with diabetes could have led to heterogeneous correlation coefficients between studies. However, in a study of 147 patients with kidney failure, where diabetic nephropathy accounted for as much as 32% of the cause of kidney failure, there was a significant correlation between TBS and BMD measured within 4 wk after transplantation.[40] TBS correlated moderately with lumbar spine BMD at baseline and 12 mo after transplantation in a recent longitudinal study of KTRs.[41] In this study, KTRs with TBS measures at high fracture risk (<1.37) and abnormal cortical and trabecular microarchitecture as measured by high-resolution peripheral computed tomography had BMD T score of >–2.5. The authors discussed that the difference in TBS and BMD measures could be due to BMD being affected by vascular calcification (false high values for BMD), not affecting TBS.[41] Potentially, degenerative changes and vascular calcifications could have affected our results as well, although a recent study disputes the widespread belief that vascular calcifications affect BMD.[42] TBS has been shown to be less affected by osteoarthritic changes than BMD, potentially explaining the discrepant results.[35,36] Lower TBS is also associated with other factors like age, sex, body mass index, smoking, steroid use, and kidney function.[9] We cannot rule out that differences in some of these factors between studies may be part of the explanation for discrepant results.

There are several strengths of this study that deserve to be mentioned. This is the first study to assess the effect of bisphosphonate on TBS in de novo KTRs. Our data are based on a previously published RCT. These longitudinal DXA data were analyzed in "one run" with the same software version and by a single certified investigator (K.G.). Some limitations are worth mentioning. The follow-up duration of 12 mo is quite short, and we do not yet possess data on fracture rates. We may not conclude from our data on the potential effect of bisphosphonates on TBS in KTRs with T scores in the "osteoporotic range" (<–2.5). TBS Z score was only available for women aged 45 y and older and men aged 40 y and older, which means 76% of our total cohort. Most of our participants were Caucasian, so our results may not be generalizable to other races (external validity).

In conclusion, TBS seems to improve quite rapidly during the first posttransplant weeks, irrespective of bone protective therapy. Treatment with ibandronate, vitamin D, and calcium did not influence TBS after a 12-mo follow-up in de novo KTRs. Deterioration in TBS and BMD after kidney transplantation was not observed in our study. TBS may complement BMD assessment in identifying KTRs with a high fracture risk.

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