

## **Bone density, microarchitecture and tissue quality long-term after kidney transplant**

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## **Authorship Page**

MJP-S, DPA, XN, AD-P and JP designed the study, assessed the calculations and wrote the manuscript. MJP-S, SH and XN did the bone procedures. MV was in charge of the study coordination.

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## **Abbreviations page**

25[OH]Vit D: 25-OH vitamin D

BMC: bone mineral content

BMD: bone mineral density

BMI: body mass index

BMSi: bone mineral strength index

DXA: dual-energy x-ray absorptiometry

eGFR: estimated glomerular filtration rate

iPTH: intact parathormone

KTR: kidney transplant recipient

TBS: trabecular bone score

## Abstract

*Background:* Bone mineral density (BMD) measured by dual-energy x-ray absorptiometry (DXA) is used to assess bone health in kidney transplant recipients (KTR). Trabecular Bone Score (TBS) and in vivo microindentation are novel techniques that directly measure trabecular microarchitecture and mechanical properties of bone at a tissue level and independently predict fracture risk. We tested the bone status of long-term KTR using all three techniques.

*Methods:* Cross-sectional study including 40 KTR with more than 10 years of follow-up and 94 healthy non-transplanted subjects as controls. BMD was measured at lumbar spine and the hip. TBS was measured by specific software on the DXA scans of lumbar spine in 39 KTR and 77 controls. Microindentation was performed at the anterior tibial face with a reference-point indenter device. Bone measurements were standardized as percentage of a reference value, expressed as bone material strength index (BMSi) units. Multivariable (age, gender and body mass index-adjusted) linear regression models were fitted to study the association between KTR and BMD/BMSi/TBS.

*Results:* BMD was lower at lumbar spine ( $0,925 \pm 0,15$  vs  $0,982 \pm 0,14$ ;  $p=0.025$ ), total hip ( $0,792 \pm 0,14$  vs  $0,902 \pm 0,13$ ;  $p<0.001$ ) and femoral neck ( $0,667 \pm 0,13$  vs  $0,775 \pm 0,12$ ;  $p<0.001$ ) in KTR than in controls. BMSi was also lower in KTR ( $79,1 \pm 7,7$  vs  $82,9 \pm 7,8$ ;  $p=0.012$ ) although this difference disappeared after adjusted model ( $p=0.145$ ). TBS was borderline lower ( $1,21 \pm 0,14$  vs  $1,3 \pm 0,15$ ; adjusted  $p=0.072$ ) in KTR.

*Conclusion:* Despite persistent decrease in BMD, trabecular microarchitecture and tissue quality remain normal in long-term KTR, suggesting important recovery of

bone health.

## Introduction

Most of the complications associated to end-stage-renal disease may be reversed after kidney transplantation (KT). However, bone mineral disturbances may persist, while new bone disorders may develop due to immunosuppressive medications such as steroids<sup>1,2</sup>. Despite its clinical relevance, bone disease in these patients is not well characterized, especially long-term after KT<sup>3</sup>.

Soon after transplantation several mineral alterations may be adjusted by normalizing renal function, but they may also persist much longer due to an autonomous parathyroid gland or limited allograft function<sup>3</sup>. In addition, there is an increased risk for fracture, both in the first years, when the dose of glucocorticoids is higher<sup>4</sup> but also several years later<sup>5,6</sup>.

Clinicians assess bone in KT recipients as in general population, by measuring areal bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA). However, this technique captures the amount of mineral but not other key aspects of bone strength, namely bone trabecular microarchitecture<sup>7,8</sup> or mechanical performance (tissue quality) as shown in several clinical situations<sup>9-12</sup>.

Since renal disease and KT combine several factors that may impact on bone tissue quality and structure, additional measurements besides DXA deserve being explored to better assess resistance to fracture in these patients<sup>13,14</sup>. Trabecular Bone Score can assess trabecular microarchitecture at the lumbar spine by analyzing DXA images with a specific software<sup>7,8</sup>. Recently, a new technique, reference-point indentation has been developed for directly assessing the mechanical properties of bone at a tissue level<sup>9-12,15,16</sup>. Microscopic indentation measures the resistance of cortical bone tissue to the opening of micro-cracks, the phenomenon closely mimicking the

initiating crack of the starting fracture<sup>15</sup>. Two main techniques have been developed, cyclic microindentation and impact microindentation. The former was used in the early clinical work<sup>10,16</sup> while the latter has been fully developed for a convenient *in vivo* clinical application<sup>10-12</sup> since simplifies the methodology for taking the measurements.

The aim of this pilot study was to analyze bone density, trabecular microarchitecture and tissue-level quality in a cohort of long-term KT patients and to test the feasibility of reference point indentation as a novel technique useful to better assess bone strength and risk of fracture in these patients.

## **Materials and Methods**

Written informed consent was obtained and the Ethics Review Board in our institution approved the study protocol.

A general clinical history, physical examination and routine laboratory measurements, including plasma and 2-hour fasting sample with levels of intact parathormone (iPTH) (*electrochemiluminescence, Roche Diagnostics GmbH, Penzberg, Germany*), and 25-OH vitamin D (25[OH]Vit D) (*ELISA, IDS, Boldon, UK*), and 24h urine sample were performed. Risk factors for fracture were recorded, and 10-year estimated absolute fracture (major and hip) risk was calculated using the Spanish version of FRAX<sup>®</sup> [*Available at: <http://www.shef.ac.uk/FRAX>*]. Spinal X-Ray was performed to detect vertebral fractures; they were assessed by two independent observers using Genant semiquantitative method<sup>17</sup> accepting grade I or above as fracture (loss >20% of vertebral height). Discrepancies were solved by consensus. DXA (BMD and Content (BMC)) was measured at lumbar spine and

proximal hip (Hologic QDR 4500 SL<sup>®</sup> (*Hologic Inc. Bedford, MA, USA*)).

Trabecular Bone Score (TBS) is a textural index that evaluates pixel gray level variations in the lumbar spine DXA image and reflect trabecular microarchitecture at the lumbar vertebrae<sup>8</sup>. Values of TBS are considered normal above 1.350, partially degraded microarchitecture between 1.200 and 1.350 and degraded below 1.200. TBS was evaluated in the same measurement regions as used for lumbar spine BMD using iNsight<sup>®</sup> v 2.1(*Med.Imaps, Merignac, France*).

Bone microindentation was performed at the anterior face of tibia with a hand held reference-point indenter device, Osteoprobe<sup>®</sup> (*Active Life Scientific, Santa Barbara, CA, USA*) (Figure 1). In brief, after local anesthesia, a preload of 10 Newton (N) followed by a 30N indentation was performed with a test probe with a conic edge of 4 $\mu$ . Average values of 8 indents were transformed by a computerized algorithm (*Active Life Technologies, Santa Barbara, CA, USA*). Five calibration indents were then performed in a polymethylmethacrylate block. Ratio between both tibia and polymethylmethacrylate measurements yield the final parameter of bone mineral strength index (BMSi) as previously described<sup>16</sup>.

The results of our KT population were compared with a control group of non-transplanted healthy individuals, selected from our reference data for microindentation. They are healthy people without history of bone disease, rheumatoid arthritis, metabolic or endocrine diseases, concurrent or prior treatment with bisphosphonates, oral corticosteroids, or any other bone-active drug.

Pearson correlations between bone (BMD and TBS) and analytical (estimated glomerular filtration rate by modified diet renal disease-4 (eGFR), 25[OH]vit D, iPTH) and BMS were studied amongst KT recipients.

Multivariable linear regression models were fitted to analyze the association between



KT status and BMS after adjustment for age, gender and body mass index (BMI). Logistic regression modeling was used to establish the association between BMS and BMD and fracture prevalence amongst KT recipients, after adjustment for age, gender, and BMI.

## Results

Cross sectional study of 40 patients with a functioning KT of more than 10 years of follow-up, free of treatments with potential impact on bone except low-dose prednisone (in twelve of them). The mean age of the 40 patients was  $63,8 \pm 11,1$  years, and 57.5% of them were female. Median [inter-quartile range (IQR)] time after transplantation was 17 years [13,2-20,7]. Mean BMI was  $26,5 \pm 3,8$  Kg/m<sup>2</sup>. Serum creatinine was  $1,5 \pm 0,6$  mg/dl, proteinuria 275 mg/24h [IQR 153-419], calcium  $9,8 \pm 0,5$  mg/dl, phosphorus  $3,5 \pm 0,7$  mg/dl, iPTH 120 ng/ml [IQR 68-210], 25[OH]vit D  $20 \pm 10,7$  ng/ml, bone alkaline phosphatase  $18,5 \pm 10,2$  U/L. 50% of cases had received anti-lymphocyte induction therapy, 97.5% were on calcineurin-inhibitors, 82.5% antimetabolites and 20% mTOR-inhibitors. All patients initially received glucocorticoids, but in 28 of them were withdrawn at a median time of 16 months [IQR 12-23] postransplant. Ten patients had received extra steroid doses (cumulative median dose 72,6 mg/kg [IQR 56,2-166,4]). The 12 patients still receiving steroids were on 5 mg prednisone daily. Median FRAX<sup>®</sup> score for the patients was 5.8 [3.3-8.4] for major fractures and 1.5 [0.8-3.3] for hip fractures.

In 13/38 (34.2%) patients, prevalent vertebral fractures were detected in the radiography although all had been subclinical. Ten patients had spinal fractures grade I and three grade II.

We measured BMD, BMSi and TBS also in 94 controls. The comparisons are showed in tables 1 (values) and 2 (linear regression analysis). Briefly, controls had better BMD at lumbar spine, total hip and femoral neck in the unadjusted analysis and when we adjusted the model by age, BMI and sex. Although we found a significant difference between KT and controls BMSi in the unadjusted analysis (mean difference [95%CI] -3,839 [-6,821 to -0,858]);  $p=0.012$ ), differences were attenuated and no longer significant after multivariable adjustment (adjusted mean difference [95%CI] -2,503 [-5,883 – 0,878]);  $p=0.145$ ). The same occurs with TBS values (see table 2).

We found a modest but statistically significant positive correlation between 25[OH]vit D levels and BMD, the strongest at total hip ( $r=0.428$ ;  $p=0.008$ ). However, no correlation between eGFR and BMD or BMSi was detected. Nor did we observe any correlation between BMD values and BMSi values. In addition, no correlation was found between TBS values and any of the parameters mentioned above. Finally, there were no differences in BMD, TBS, or BMSi between patients on glucocorticoids vs those steroid-free, neither a correlation with cumulative glucocorticoid dose (data not shown).

Regarding BMD measurements between KT patients with vertebral fractures and those without, we found no statistically significant differences at any of the assessed sites (lumbar spine, femoral neck and total hip). No differences were found neither in terms of BMSi or TBS.

## Discussion

This study describes bone status of long-term KT recipients, showing a high prevalence of secondary hyperparathyroidism and vitamin D deficiency. Bone mineral density was decreased vs controls while trabecular microarchitecture was comparable. In terms of bone quality, as measured by microindentation, KT recipients were not different from controls. Overall, these results show an almost complete normalization of bone long after KT, although some decrease in bone density and metabolic changes still remain. To our knowledge, this is the first study where a comprehensive assessment of bone health at different levels, from quantity to structure and tissue quality has been performed.

Although KT reverses many of the problems not corrected by dialysis, as shown by the decrease in fracture risk one to two years after transplant<sup>4-6,18</sup>, some of the characteristics of bone disease may persist, with potential increased morbidity, mortality and costs<sup>19</sup>. Our results confirm that secondary hyperparathyroidism remains in long-term KT patients despite good renal function, with elevated PTH levels, normocalcemia and normophosphatemia<sup>3,20</sup>. This raised PTH may be partially explained by lower vitamin D levels<sup>21</sup>. In spite of living in a Mediterranean region, our KT recipients have very low levels of 25-OH-vitamin D, even lower than has been described<sup>22</sup>. We also observed that patients with higher levels of 25-OH-vitamin D have higher BMD without any influence in TBS or BMSi values.

Renal allograft recipients experience a rapid bone density loss, especially during the first months after KT, attributable to persistent hyperparathyroidism, but also because immunosuppressive therapy is deleterious since increases bone resorption and decreases bone formation<sup>23</sup>. This results in a 3-fold higher overall fracture risk in KT

compared to healthy individuals<sup>4,18</sup>, with a remarkable 30% increase during the first years after transplant compared to patients on dialysis<sup>4</sup>. However, our long-term KT population are not at high risk for fracture according to FRAX<sup>®</sup> score.

On the other hand, the prevalence of asymptomatic fractures in long-term transplant patients has been established between 30-60%<sup>24-26</sup>, similar to the detected rate (one third) in our cohort, although the majority of them were only vertebral deformities. These vertebral fractures may present in KT recipients with normal or osteopenic values of DXA, similar to general population<sup>24,27</sup>. We found lower BMD values both at lumbar spine and also at hip between KT patients and controls.

Nevertheless, BMD is not the sole parameter apt to evaluate bone strength, i.e. capacity of bone of absorbing energy before fracturing. In fact, elasticity, spatial trabecular disposition and concentration, collagen quality and other factors are also responsible for bone strength. In fact, bone fractures have been evidenced also in the presence of normal or only slightly reduced BMD in the general population<sup>28</sup>. In a previous study, long-term recipients with good kidney function had no alteration in bone histology, despite slight increase in PTH<sup>29</sup>. However, as DXA is not the gold standard for estimating bone health in renal patients<sup>24</sup>, and bone biopsy is a very invasive technique rarely performed in clinics<sup>29</sup>, other measurements are convenient to complete the bone assessment in these cases. Trabecular Bone Score measures the trabecular compartment microarchitecture in the vertebrae, a demonstrated independent predictor of fracture risk<sup>7</sup>. It has been recently demonstrated that KT recipients have lower values of TBS than general population (measured early after transplantation) and it is a risk factor for future fracture<sup>30</sup>. However, our patients presented with similar TBS values than controls, demonstrating an almost complete recovery in bone health more than ten years after transplantation. Moreover, here we

demonstrate that microindentation, a convenient minimally invasive technique to assess bone quality at a tissue level, that also independently predicts the risk of fracture, may also be used in KT recipients. Microindentation has been proved in other cohorts where risk of fracture is only partially captured by DXA: atypical femoral fractures<sup>9</sup>, postmenopausal women with diabetes<sup>10</sup>, fragility fractures with osteopenia<sup>11</sup>, glucocorticoids<sup>12</sup> or in Scandinavian women at high risk of fracture<sup>28</sup>. Our patients presented similar BMSi values than the general population adjusted by age, gender and BMI. This could be related to the fact that we did not achieve enough power to detect differences between both cohorts due to more variability in BMSi values than in BMD values. However, finding no differences probably reflects that if there is bone affectation in this population, this is not much relevant and long-term KT patients present similar bone tissue material properties than controls, despite its rate of hyperparathyroidism and vitamin D deficiency. This is consistent with previous data showing that mineral and bone disorder is temporary in KT patients with a rapid steroid reduction or withdrawal after kidney transplantation<sup>1</sup>, especially at the central skeleton<sup>2</sup>. It is likely that the bone derangement is recovered long-term after transplantation without active glucocorticoids treatment.

The main limitations of our study are the small sample size and the cross-sectional design. Moreover, these recipients might have better bone health because they represent a special cohort with more than 10 years of follow-up and bone properties could potentially be worse in individuals who do not survive as long. However, the assessment of bone quality by microindentation is a novel technique capturing additional information on bone strength, has never used in renal patients to date. In several groups of patients has been associated with fractures, independently of BMD<sup>9-12,28</sup> what gives potential clinical applicability for a comprehensive assessment

of bone in KT patients. In any case its ultimate value for the assessment of fracture risk and monitoring interventions remains to be established in larger longitudinal studies.

In conclusion, BMD was lower in KT than in our matched controls, but trabecular microarchitecture and tissue quality, assessed with in vivo microindentation, appears to be recovered at levels similar to controls in spite of a high prevalence of secondary hyperparathyroidism and vitamin D insufficiency. Therefore long after KT some key determinants of bone strength are fully normalized. The assessment of these patients should be done by measuring the different determinants of bone fragility, i.e., fracture risk.

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**Table 1.** Bone variables in kidney transplant patients and controls.

	KT patients		Controls		p
	n		n		
<b>Age (years, mean <math>\pm</math> sd)</b>	40	63,8 $\pm$ 11,1	94	50,2 $\pm$ 16	<0,001
<b>Gender (female, n)</b>	40	23	94	74	0.012
<b>BMI (Kg/cm<sup>2</sup>, mean <math>\pm</math> sd)</b>	40	26,5 $\pm$ 3,8	74	24,8 $\pm$ 4	0.031
<b>Prevalent vertebral fractures</b>	40	13	94	0	
<b>Bone mineral density by DXA</b>					
Lumbar (gr/cm <sup>2</sup> )	39	0,925 $\pm$ 0,15	72	0,982 $\pm$ 0,14	0.050
Total Hip (gr/cm <sup>2</sup> )	37	0,792 $\pm$ 0,14	68	0,902 $\pm$ 0,13	<0.001
Femoral Neck (gr/cm <sup>2</sup> )	37	0,667 $\pm$ 0,13	72	0,775 $\pm$ 0,12	<0.001
<b>Trabecular Bone Score</b>	39	1,21 $\pm$ 0,14	77	1,3 $\pm$ 0,15	0.072
<b>Reference-point indentation</b>					
Bone Material Strength index (units)	38	79,1 $\pm$ 7,7	93	82,9 $\pm$ 7,8	0.145

KT: Kidney transplantation. Sd: Standard deviation. BMI: Body mass index.

DXA, dual-energy X-Ray absorptiometry

**Table 2.** Linear regression analysis, crude and adjusted, for bone parameters.

Dependent variable is the fact of being transplanted.

	Crude analysis			Adjusted analysis (age, gender and BMI)		
	$\beta$	IC (95%)	p	$\beta$	IC (95%)	p
<b>LS BMD</b>	-0,057	-1,979 to 0,000	0.050	-0,066	-0,123 to -0,008	0.025
<b>TH BMD</b>	-0,110	-0,165 to -0,055	<0.001	-0,116	-0,158 to -0,073	<0.001
<b>FN BMD</b>	-0,108	-0,157 to -0,060	<0.001	-0,108	-0,146 to -0,071	<0.001
<b>BMSi</b>	-3,839	-6,821 to -0,858	0.012	-2,503	-5,883 to 0,878	0.145
<b>TBS</b>	-0,095	-0,152 to -0,038	0.001	-0,056	-0,117 to 0,005	0.072

LS, lumbar spine; BMD, bone mineral density; TH, total hip; FN, femoral neck;

BMSi, bone mineral strength index; TBS, trabecular bone score.

### **Figure 1 legend**

Microindentation technical device (Osteoprobe®). General view of the technique in a patient using the handheld reference-point indenter device Osteoprobe®. Results are expressed as Bone Mineral Strength index (BMSi). For details refer to Methods section.

**Figure 1**

