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RESEARCH

Impact of corticosteroid withdrawal on bone mineral density after kidney transplantation

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Abstract

Background Bone abnormalities are common after kidney transplantation (KTx) and are associated with an increased risk of fractures. The pathophysiology of post-KTx bone disorders is multifactorial, with corticosteroid (CS) therapy being a contributor to the loss of bone mineral density (BMD). This study aimed to evaluate the impact of CS withdrawal versus continued CS therapy on BMD evolution in a kidney transplant recipients (KTRs) cohort.

Methods We retrospectively analyzed BMD data from 132 patients who underwent KTx between 2005 and 2021. BMD was assessed using dual-energy X-ray absorptiometry at the time of KTx (T0) and two-years post-KTx (2yT). Patients were categorized into two groups: those who discontinued CS (CS−) within the first-year post KTx and those who continued CS therapy (CS+).

Results The mean age at KTx was 52.2 (± 12.6) years, and 62.1% of the patients were male. Overall, BMD increased significantly at the lumbar spine (LS) but decreased at the radius at 2yT, while BMD at the hip site remained stable. CS was discontinued in 44.7% of patients between T0 and 2yT, with an average discontinuation time of 6.3 (± 4.9) months post-KTx. The CS− group showed significant BMD improvements at LS and hip sites. In a multivariate analysis, a higher cumulative CS dose was independently associated with a larger BMD decline.

Conclusions CS withdrawal after KTx positively impacts BMD, while higher cumulative CS doses are associated with a greater BMD loss. These findings underscore the importance of minimizing CS exposure to preserve bone health in KTRs.

Keywords Kidney transplantation · Corticosteroids withdrawal · Bone mineral density · Fractures

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Introduction

Kidney transplantation (KTx) is the optimal treatment for patients with end-stage renal disease (ESRD) [1, 2]. Advances in immunosuppressive therapies have significantly improved the one-year survival rate of kidney allografts [3]. Furthermore, enhancing long-term survival and quality of life for kidney transplant recipients (KTRs) remains challenging. This involves preventing cardiovascular diseases, cancers, and improving bone health in this high-risk population.

Mineral and bone disorders (MBD) are frequent in chronic kidney disease (CKD) patients and often persist, even after successful KTx [4–7]. Approximately 10% of KTRs will experience one or more fractures during their lifetime [8, 9]. These fractures are associated with increased risk of morbidity, hospitalizations and mortality [10]. The pathophysiology of bone and mineral abnormalities post-KTx is complex [11]. Specific pathological processes related to KTx [12], such as hypophosphatemia and decreased bone turnover induced by corticosteroids (CS), contribute significantly to the increased fracture risk in this population [13, 14].

Protocols for early CS withdrawal (ECSW) have been employed to improve bone prognosis post-KTx [15, 16]. However, current literature on the long-term impact of CS withdrawal post KTx on bone health is limited and yields divergent results regarding effects on bone mineral density (BMD) outcomes and fracture incidence [9, 17]. Furthermore, these studies rarely consider i) the total cumulative dose of CS received by the patient; ii) the withdrawal of CS within the first year of KTx and iii) the impact of remineralization treatment.

Therefore, in our transplant cohort, we conducted a retrospective analysis to evaluate the impact of CS withdrawal within the first year post-KTx on BMD evolution at two years (2yT) as the primary outcome. In this analysis, the cumulative CS dose and the remineralization therapy during the follow-up period were considered.

Patients and methods

Study protocol

This retrospective analysis is part of a larger prospective cohort study (ClinicalTrials.gov identifier: NCT03764124) including patients from the University Hospital of Liège (CHU-ULiège) who underwent their first single KTx between January 1, 2005, and February 28, 2021. The majority of the cohort (n = 599) underwent dual X-ray absorptiometry scan (DXA) evaluation within the first year post-KTx. However, to minimize the impact of rapid bone changes observed early after KTx, we included only patients who had a baseline DXA scan performed within 65 days post-KTx (T0). A second evaluation was conducted at 2 years (± 90 days) post-KTx (2yT). For patients who did not have a bone density measurement at 2yT but had two DXA scans—one before and one after 2yT (within a 4-year window post-KTx)—a linear interpolation model was used to estimate bone density at 2yT. Exclusion criteria included patients under 18 years of age, those receiving remineralization treatment before KTx, and those who experienced graft failure, death, or were lost to follow-up within 2yT post-KTx (Fig. 1).

The following clinical characteristics were collected from an electronic database within the defined period of interest: age, gender, diabetes status, hypertension, body

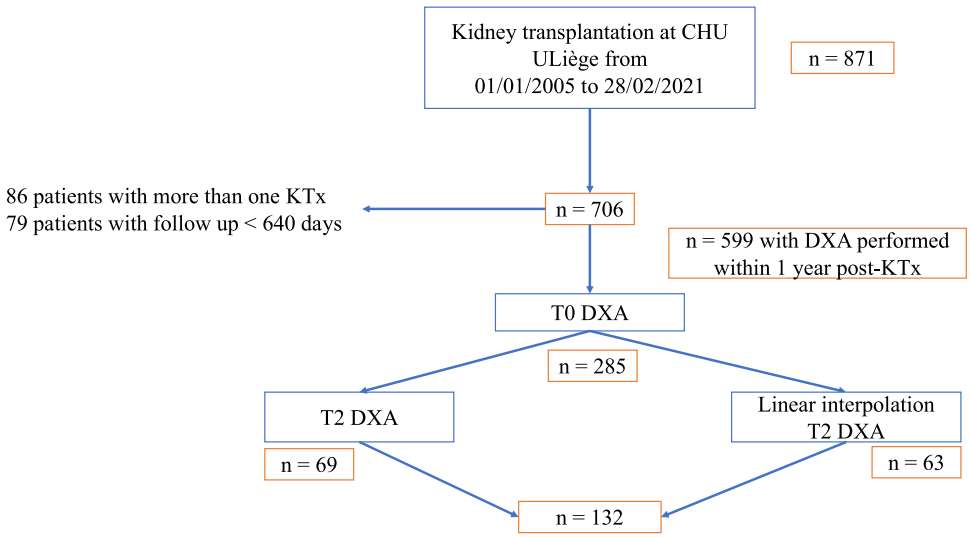

Fig. 1 Flowchart. The flowchart illustrates the sequential steps for cohort selection, including inclusion and exclusion criteria, starting from the initial population included from 01/01/2005 to 28/02/2021. *CHU* university hospital centre, *DXA* dual-energy X-ray absorptiometry, *KTx* kidney transplantation, *wo* without

mass index (BMI), cause of kidney failure, type of dialysis, dialysis vintage and history of parathyroidectomy (PTHx). The occurrence of major osteoporotic fractures (MOF), defined as hip, humeral, forearm, or vertebral fractures, was reviewed in patients' files. These fractures could be either clinically significant or incidentally found through imaging techniques performed for other reasons. Initiation of anti-resorptive therapy (i.e., bisphosphonate or denosumab) or PTHx between T0 and 2yT were also noted. The primary outcome was the evolution of BMD at different sites: lumbar spine (LS), total hip (TH), femoral neck (FN), and radius (total, distal one-third (1/3), ultradistal (UD)).

Biological data and bone densitometry

Biological analyses included measurements of 25-hydroxy vitamin D (25-OH vitD) (ng/mL), calcium (mmol/L), phosphate (mmol/L), parathormone (PTH) (ng/L—PTH was expressed as the upper limit of normal [ULN]), and the bone formation biomarker, bone alkaline phosphatase (BALP) (µg/L). BALP, 25-OH vitD and 3rd generation PTH were measured with the DiaSorin Liaison ECLIA instrument.

Participants underwent BMD measurements using DXA (Discovery; Hologic, Waltham, MA, USA) at the LS, FN, TH, and radius (total, distal 1/3 and UD). All DXA scans were analysed at two certified sites (Brull and Sart-Tilman) within the same university hospital. BMD results were expressed in g/cm^2 and T-score. A variation in BMD exceeding 2% was used as the threshold for determining bone loss or gain at 2yT, corresponding to the intra-individual measurement variation (least significant change [LSC]) [18, 19]. Osteoporosis was defined as a T-score ≤ -2.5 and osteopenia as a T-score < -1 and > -2.5 [20].

Corticosteroid treatment

Standard CS administration at our institution involves an induction phase with an intravenous (IV) injection of 625 mg methylprednisolone at the time of KTx associated with either basiliximab or anti-thymoglobulin. Following this, a maintenance dose of methylprednisolone is initiated at 16 mg, gradually reduced by 4 mg every 3 weeks, reaching 4 mg after 3 months. Maintenance immunosuppressive therapy includes calcineurin inhibitors (tacrolimus or cyclosporine) and antimetabolites (mycophenolate mofetil or azathioprin). The decision to withdraw CS is conventionally based on (i) the results of a protocol renal biopsy performed at 3 months post-KTx and (ii) immunological risk of the patient. If CS withdrawal is decided on the 3-month biopsy results, the tapering process is gradual. Patients were divided into 2 groups based on CS withdrawal status within the first year of KTx: CS− (withdrawn) and CS+ (not withdrawn). Some patients also received CS treatment for rejection (IV methylprednisolone), and this dose was included in the cumulative dose calculation performed for every patient. The cumulative CS dose (methylprednisolone equivalent) was measured using a previously published calculator [21]. This calculator aims to standardize CS dose assessment and was validated through simulation exercises, showing a mean error of less than 7% even with incomplete data [21].

Statistical analyses

Data were presented as mean ± standard deviation (SD) when the distribution was normal and as median with interquartile range (IQR) [quartile 1–quartile 3] when it was not. Normality was assessed using the Kolmogorov–Smirnov test. The evolution of BMD parameters between T0 and 2yT was analysed using the Student's t-test. BMD changes in g/cm^2 or percentage were reported as proportions and 95% confidence intervals (CI). Correlations between absolute differences (delta) in BMD and demographic or other parameters were calculated using Spearman's method for continuous variables and the Student's t-test for qualitative variables. The change in categories between T0 and 2yT, from the osteoporotic class to the osteopenia class, was assessed using multinomial logistic regression.

For patients without bone density measurements at 2yT but with two DXA scans—one performed between day (D) 66 and D640, and the other between D820 and D1460 since KTx —a linear interpolation model was used to estimate bone density at 2yT (D730). The analysis was conducted on the entire cohort (n = 132), and sensitivity analyses were performed, focusing on the population of patients with strict measurements at both T0 and 2yT (n = 69), excluding those with interpolated values (n = 63).

To study the impact of the cumulative dose of CS or the use of remineralization treatment on the evolution of BMD, multivariate linear regression was used for differences in g/cm^2, and multivariate logistic regression was used for changes greater than 2%. The multivariate regression model included parameters affecting BMD changes, such as age, gender, dialysis vintage, CS dose (log-transformed) and presence of remineralization treatment. Results are considered significant at a 5% uncertainty level ($p < 0.05$). 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

Out of the 871 patients who underwent KTx during the study period, 132 were eligible for inclusion (see flow chart in Fig. 1). The characteristics of the population at the time of KTx are shown in Table 1. Mean age was 52.2 (± 12.6)

Table 1 Clinical and bone densitometry characteristics of the population (n = 132)

	Total cohort n = 132	CS− patients n = 59	CS+ patients n = 73	*p* value
Recipient age (years) (median [IQR])	54.9 [44.2–61.9]	55.1 [44.7–62.7]	54.9 [43.8–60.4]	0.5
Gender (% male)	62.1	66.1	58.9	0.4
ESRD causes (%)				
Diabetic/hypertensive nephropathy	15.6	13.6	16.4	
Glomerular/vasculitis nephropathy	34.9	37.3	32.9	
Tubulo-interstitial nephropathy	12.1	5.1	17.8	
Cysts/genetic nephropathy	20.4	25.4	16.4	
Others	2.2	3.4	1.4	
Unknown nephropathy	15.1	15.2	15	0.6
BMI at KTx (kg/m^2) (mean ± SD)	25.1 ± 4.6	25.6 ± 4.8	24.6 ± 4.4	0.2
Dialysis (%)	85.6	81.4	89	0.2
Dialysis vintage (months) (median [IQR])	20.1 [8.7–36.4]	12.4 [2.2–27.3]	24.1 [10.8–41.4]	**0.004**
Donor age (years) (median [IQR])	46 [33–55]	41 [30–54]	47 [39–55]	0.08
Lowest creatininemia within 3 months (mg/dl) (median [IQR])	1.1 [0.91–1.27]	1.1 [0.87–1.31]	1.1 [0.94–1.24]	0.9
Fracture (%)	13.6	13.6	13.7	0.9
Delay fracture post KTx (years) (median [IQR])	4.2 [1.8–5.9]	4.1 [1.1–6.1]	4.2 [1.8–5.0]	1
Parathyroidectomy (%)	6.8	5.12	8.1	0.5
Remineralization treatment (%)	31.8	28.8	34.3	0.5
Rejection rate (%)	22.7	20.3	24.7	0.6
CS cumulative dose (mg) (median [IQR])	3563.5 [1831–4209]	1769 [1619–2446]	4083 [3759–4611]	**< 0.0001**
T-score LS at T0	− 1.48 ± 1.51	− 1.36 ± 1.63	− 1.57 ± 1.40	0.4
T-score TH at T0	− 1.16 ± 0.96	− 1.17 ± 1.03	− 1.15 ± 0.90	0.9
T-score FN at T0	− 1.43 ± 1.01	− 1.52 ± 1.02	− 1.36 ± 1.02	0.4
T-score total radius at T0	− 1.63 ± 1.41	− 1.67 ± 1.52	− 1.59 ± 1.29	0.8

Bold values indicates the statistical difference

p value compared CS+ and CS− groups (*t*-test or Mann Whitney/Wilcoxon). Parathyroidectomy and remineralization treatment given between T0 and 2yT

BMI: body mass index; CS: corticosteroids; CS−: weaning of corticosteroids; CS+ : not weaned of corticosteroids; ESRD: end stage renal disease; FN: femoral neck; KTx: kidney transplantation; LS: lumbar spine; SD: standard deviation; TH: total hip

years, and 62.1% of the patients were male. Mean BMI was 25.1 (± 4.58) kg/m^2. The most common cause of CKD was glomerulopathy/vasculitis (34.9%), followed by cystic/genetic nephropathy (20.5%). Other causes included diabetic/hypertensive nephropathy (15.1%), interstitial nephritis (12.1%), other etiologies (2.3%), and unknown etiologies (15.1%). Eighty-three percent of patients had hypertension, and 21% had diabetes. At the time of KTx, 85.6% of patients were on chronic dialysis, with a median dialysis vintage of 20.1 [8.7–36.4] months. Fourteen percent of the patients received pre-emptive transplants. Remineralization treatment was initiated in 31.8% of patients between T0 and 2yT. At 2yT, the median cumulative dose of CS was 3563.5 [1831–4209] mg. CS were successfully weaned off in 44.7% of patients, with withdrawal occurring an average of 6.7 [5.2–10.2] months post-KTx. Over the entire follow-up period of 8.9 [4.7–11.9] years, 13.6% of patients experienced a fracture, occurring on average 4.2 [1.8–5.9] years after KTx. The clinical cohort characteristics were not different between the population with or without linear interpolation except regarding the rejection rate (lower in the interpolated group) and T-score at the total radius site (higher in the interpolated group) (Supplementary Table 1).

The Table 2 summarizes the biological parameters at T0 and 2yT. At 2yT, there was a significant decrease in PTH levels (from 5.2 to 1.4 times the ULN, $p < 0.0001$), a significant increase in 25-OH vitD levels (from 25 to 30 ng/mL, $p < 0.0001$), an increase in calcium (from 2.34 to 2.45 mmol/L, $p < 0.0001$), and a decrease in phosphate (from 1.81 to 1.0 mmol/L, $p < 0.0001$) and BALP (from 14.9 to 13.1 µg/L, $p = 0.02$).

Regarding BMD analysis, the median time for the T0 and 2yT measurements was 32.5 [7–54] days post-KTx and 762 [729–786] post-KTx, respectively, with a mean 24.3 (± 3.1) months between the two exams. For the whole cohort, at T0, the mean T-score values were − 1.48 ± 1.51 at LS; − 1.16

Table 2 Biological characteristics of the population at the time of kidney transplantation and two years after

	N	T0	2yT	*p* value
PTH (ULN) (median [IQR])	111/125	5.2 [3.2–8.6]	1.4 [1.1–1.9]	**< 0.0001**
25-OH-vitD (ng/mL) (median [IQR])	103/129	25.0 [16.0–32.8]	30.0 [25.7–36.0]	**< 0.0001**
Calcium (mmol/L) (mean ± SD)	130/131	2.34 ± 0.20	2.45 ± 0. 12	**< 0.0001**
Phosphates (mmol/L) (median [IQR])	115/132	1.81 [1.4–7.8]	1.0 [0.8–3.7]	**< 0.0001**
BALP (µg/L) (median [IQR])	56/88	14.9 [10.8–24.0]	13.1 [9.7–20.0]	**0.02**

Bold values indicates the statistical difference

25-OH-vitD: 25-Hydroxy-vitamin D; BALP: Bone alkaline phosphatase; IQR: interquartile range; PTH: Parathormone; N: Number of patients by group T0/2yT; ULN: Upper limit of normal

± 0.96 at TH; − 1.43 ± 1.01 at FN and − 1.63 ± 1.41 at total radius site (Table 1). At T0, osteoporosis was observed in 8% to 27% of patients, depending on the skeletal site: LS 27.0%, TH 7.9%, FN 13.4%, and total radius 20.3%. Similarly, osteopenia was detected in 40% to 55% of patients, with prevalence varying by skeletal site: LS 39.2%, TH 51.2%, FN 55.1%, and total radius 50.0%. The T0 DXA assessment revealed significantly lower T-scores at all three sites ($p < 0.0002$) in patients intended to receive remineralization treatment compared to those who did not. The mean value for respectively LS, TH and FN were − 2.6 (± 1.2) versus − 0.96 (± 1.3); − 1.6 (± 0.9) versus − 0.91 (± 0.97); − 2 (± 0.75) versus − 1.2 (± 1). A significant gain in BMD was observed between T0 and 2yT at the LS ($p = 0.03$), while a significant loss was observed at the radius (total and 1/3 distal) ($p = 0.003$ and $p = 0.0005$). No significant changes were observed at other sites (Table 3). For patients without linear interpolation (n = 69), at 2yT, the prevalence of osteoporosis by site was as follows: LS 22.1%, TH 6%, FN 7.4%, and total radius 17.8%. For osteopenia by site, the prevalence was: LS 32.4%, TH 51.5%, FN 58.8%, and total radius 48.9%. Only at the LS site was there a significantly greater chance for patients in the osteoporosis category at T0 to transition to the osteopenia stage at 2yT ($p = 0.003$). No significant differences were observed at the other sites.

In the entire cohort, univariable analysis found no clinical or biological baseline parameters correlated with BMD changes at the LS or hip sites, except for age and TH losses (r = 0.213; $p = 0.02$) and cumulative CS dose, which showed a positive correlation with BMD losses at the LS (r = 0.363; $p < 0.0001$), TH (r = 0.311; $p = 0.0004$), and FN (r = 0.269; $p = 0.002$) levels. Conversely, at the radius site, significant positive correlations were found between age, BMI, and BMD losses (total radius site: r = 0.263 and 0.309; $p = 0.03$ and 0.01 for age and BMI, respectively), while no correlation was observed with the cumulative CS dose. Additionally, a positive correlation was observed between PTH levels at 2yT and total radius bone loss (r = 0.351; $p = 0.003$).

Table 3 Comparison of bone mineral density at different sites in the studied population at T0 and 2yT

	Total cohort n = 132	*p* value	CS− n = 59	*p* value	CS+ n = 73	*p* value
BMD LS T0 (n = 131)	***0.903 ± 0.164***	**0.03**	***0.906 ± 0.169***	**0.0003**	0.900 ± 0.161	
BMD LS 2yT	***0.917 ± 0.153***		***0.943 ± 0.155***		0.897 ± 0.149	0.8
BMD TH T0 (n = 127)	0.838 ± 0.155		***0.828 ± 0.160***	**0.02**	0.846 ± 0.151	
BMD TH 2yT	0.846 ± 0.150	0.2	***0.851 ± 0.153***		0.841 ± 0.149	0.5
BMD FN T0 (n = 127)	0.709 ± 0.132	0.2	***0.699 ± 0.139***	**0.01**	0.718 ± 0.127	0.6
BMD FN 2yT	0.716 ± 0.128		***0.718 ± 0.133***		0.714 ± 0.125	
BMD radius total T0 (n = 69)	*0.543 ± 0.096*	**0.003**	*0.544 ± 0.091*	**0.02**	0.542 ± 0.102	
BMD radius total 2yT	*0.531 ± 0.098*		*0.532 ± 0.099*		0.531 ± 0.098	0.06
BMD radius distal 1/3 T0 (n = 69)	*0.695 ± 0.109*	**0.0005**	*0.701 ± 0.099*	**0.002**	0.690 ± 0.118	
BMD radius distal 1/3 2yT	*0.677 ± 0.110*		*0.677 ± 0.117*		0.675 ± 0.112	0.06
BMD UD radius T0 (n = 69)	0.393 ± 0.086	0.51	0.392 ± 0.083	0.7	0.394 ± 0.090	
BMD UD radius 2yT	0.389 ± 0.096		0.396 ± 0.110		0.383 ± 0.110	0.05

Bold values indicates the statistical difference

In bolditalic: significant improvement of BMD. In italic: significant decrease of BMD

2yT: two years post kidney transplantation; BMD: bone mineral density expressed in g/cm^2; CS: corticosteroids; LS: lumbar spine; T0: time of kidney transplantation; TH: total hip; FN: femoral neck; SD: standard deviation; UD: ultra-distal radius

When comparing the CS− and CS+ groups, the only significant difference at T0 was the dialysis vintage, which was longer in the CS+ group (Table 1). As expected, the cumulative dose at 2yT differed, with 1769 [1619–2446] mg for the CS− group and 4083 [3759–4611] mg for the CS+ group ($p < 0.0001$). Comparing the CS− and CS+ groups, a significant gain in BMD was observed at the LS, FN, and TH in the CS− group whereas no significant changes were observed in the CS+ group and a significant decreased in the CS− for total and 1/3 radius (Table 3). The sensitivity analysis focusing on the population without linear interpolation (n = 69) yielded similar results, except at the FN and UD radius sites. Numerical improvements were observed at the FN site in the CS− group, though these were not statistically significant, while a significant decrease in BMD at 2yT was observed at the UD radius site in the CS+ group (Supplementary Table 2).

To examine the impact of cumulative CS dose on BMD changes (greater than 2%) in the entire cohort, a multivariate model was used, adjusting for known factors influencing BMD (age, gender, dialysis vintage, cumulative CS dose, and the presence of remineralization treatment). At the three major sites (LS, TH, FN), higher cumulative CS doses were associated with larger BMD losses between T0 and 2yT (for LS: OR: 6.2, 95% CI 2.4–16.4; $p = 0.0002$). No other parameters in the model were significantly linked to BMD changes at the LS. Conversely, at the hip level, the risk of BMD loss increased with both cumulative CS dose and age, while no other parameters were found to be associated with BMD changes (for TH, OR for CS: 4.9, 95% CI 1.8–13.5; $p = 0.002$, and OR for age: 1.049, 95% CI 1.01–1.09; $p = 0.01$). For the class change from T0 to 2yT at the LS site, discontinuation of CS increased the chances of transitioning from the osteoporotic stage to the osteopenia stage ($p = 0.003$).

At the radius sites (total and distal 1/3), significant bone loss was observed between T0 and 2yT, which was unaffected by cumulative CS dose or other model parameters. In a sensitivity analysis excluding patients with linear interpolation (n = 69), the association remained significant at the three major sites (LS, TH, FN), with higher cumulative CS doses being linked to greater BMD losses between T0 and 2yT (for LS: OR: 6.7, 95% CI 1.6–27.0; $p = 0.009$).

Discussion

Our study included 132 KTRs, with a focus on analyzing the evolution of BMD over the first two years post-KTx. In the overall population, a significant BMD gain was observed at the LS between T0 and 2yT, while a significant loss occurred at the radius (total and 1/3 distal). No significant changes were detected at other skeletal sites. The biomarker evolution post-KTx was consistent with previous data from the literature [22], showing lower PTH levels and higher vitamin D levels at 2yT compared to T0, alongside significant changes in calcium, phosphate, and BALP levels. Approximately half of the cohort discontinued CS therapy, primarily within the first year post-KTx. Both the weaned and non-weaned groups were comparable, except for differences in dialysis vintage and cumulative CS doses. When comparing the CS− and CS+ groups, the CS− group showed a statistically significant gain in BMD at the major sites (LS, TH, FN), whereas no significant changes were observed in the CS+ group between the two time points. Higher cumulative CS doses were independently associated with greater BMD losses between T0 and 2yT at the three major sites. The absence of BMD improvement at the LS in the CS+ group in our cohort underscores the importance of CS weaning in selected patients.

The use of CS in KTx is common, with tapering often pursued due to the well-documented metabolic and bone-related side effects. These side effects are closely linked to the cumulative dose of CS administered [23]. CS profoundly suppress osteoblast function, increase osteoblast apoptosis, enhance osteoclast activity, decrease gastrointestinal calcium absorption and gonadal hormones, resulting in a reduced bone formation with an overall increased risk of fracture [23]. International guidelines recommend tapering CS within the first week post-KTx if a decision is made to withdraw them, as studies have shown an increased risk of rejection associated with late steroid withdrawal [24]. However, a meta-analysis by Pascual et al. concluded that CS tapering between 3 to 6 months post-KTx was not associated with increased rates of rejection, except in patients treated with cyclosporine instead of tacrolimus [25].

As demonstrated by other groups, we found a significant gain in BMD at the LS at 2yT post-KTx, while a significant loss was observed at the radius (total and 1/3 distal). In a prospective observational cohort comprising 69 KTRs with a CS minimization protocol similar to ours, Evenepoel et al. [18] demonstrated a significant BMD gain at the LS 5 years post-KTx (with a non-significant decrease at 1 year). No significant changes at the hip were noted in that study either. In their study, CS exposure was associated with BMD losses at LS and FN. In contrast to the study by Evenepoel et al., our cohort included patients with lower LS BMD at the time of KTx, where CS weaning was possible within the first year post-KTx in roughly 50% of the patients. This allowed us to compare patients following a standard CS minimization protocol with those who underwent CS weaning. Although remineralization treatment was used consistently throughout the study, it was identical between the CS− and CS+ groups.

Another retrospective observational Japanese study involving 34 KTRs demonstrated that with a different CS withdrawal scheme, there was a significant decrease in BMD

at the hip site between 4 and 8 months. However, BMD levels returned to those recorded before KTx within 12 to 24 months, and no decrease was observed at the LS [26]. A notable difference compared to our study is the high rate of preemptive KTx (41%) in this study, with patients having normal BMD levels at the time of KTx, which limits the generalizability of their findings. Additionally, the study did not include a comparison with a complete CS weaning group, whereas we were able to demonstrate an improvement in BMD at the major sites among those who underwent CS weaning.

Moreover, Segaud et al. [27] demonstrated in a cohort of KTRs with either ECSW or other CS protocols that longer CS exposure negatively affected LS and hip BMD. However, the absence of a complete group for late CS tapering or a continuous CS group, as well as the lack of cumulative CS dose data and the delay in bone evaluation (with the first assessment performed at 9 months post-KTx), limits direct comparisons with our results. They also reported a high rate of osteoporosis (40%), which may have been overestimated due to the late timing of the assessment after KTx. As demonstrated by Chandran et al., significant changes can already be observed between D0 and 6 months post-KTx [28].

In a non-randomized controlled trial (RCT) Iyer et al. demonstrated in a 47 KTR cohort that ECSW initiated three days after KTx was not associated with significant changes in BMD at the LS or hip after one year [15]. A notable difference compared to our study is the high rate of preemptive KTx (51%) and the rate of living donation (81%) in this study, with patients having normal BMD levels at the time of KTx, which limits the generalizability of their findings. Additionally, the study did not include a comparison with a non-CS weaning group.

Finally, in a RCT published over a decade ago, comparing a continuous CS protocol with a CS withdrawal protocol, Ing et al. demonstrated in a cohort of 87 KTRs that the CS withdrawal protocol had beneficial effects on LS and hip BMD, with significant improvements observed in the CS-sparing group [29]. However, several limitations should be noted, including the 15-month delay between KTx and the first BMD assessment, during which significant changes could have already occurred, the use of a non-standard CS withdrawal scheme, and the absence of CS cumulative dose data after enrolment. Nonetheless, this study, like ours, highlights the potential impact of late CS withdrawal on bone health.

Regarding the evolution of radius BMD, a significant loss was observed between T0 and 2yT at both the total and distal 1/3 radius ($p = 0.003$ and $p = 0.0005$, respectively), particularly in the group with CS withdrawal. The lack of CS weaning effect on radius BMD evolution suggests that cortical bone at this site may be less responsive to CS compared to trabecular bone. Studies have highlighted the specificity of cortical bone loss compared to trabecular bone in CKD patients, with a decrease in cortical density and thickness observed after a median follow-up of 1.5 years in patients with CKD stages 2 to 5 [30]. Moreover in KTRs, Iyer et al. demonstrated that a ECSW was associated with a significant decrease in BMD at the radius at 1 year post KTx [15]. This outcome underscores the complex nature of bone metabolism and suggests that factors beyond CS use may contribute to site-specific variations in BMD changes. Evenepoel et al. [18] demonstrated a significant loss of BMD at the radius site at 1 year, which was maintained at 5 years, in their KTR cohort. The positive correlation between PTH levels at 2yT and total radius bone loss ($r = 0.351$; $p = 0.003$) highlights the critical importance of controlling phospho-calcic parameters in the peri-KTx period to mitigate bone loss, as it was also demonstrated in the study by Evenepoel et al. [18]. Proper management of these parameters might provide additional protection against bone deterioration [12, 31].

While remineralization treatment was initiated in 31% of patients, it did not show a significant beneficial effect on BMD evolution in our population. This contrasts with the findings of the study by Segaud et al. [27], which compared patients with and without remineralization treatment. Their results demonstrated significantly greater improvements in the bisphosphonate-treated group compared to the untreated group. However, significant improvements at major sites were also observed in the untreated group. Differences in study design and timing of assessments between the two studies may explain these discrepancies. Other studies have failed to show a significant benefit of bisphosphonates on BMD after KTx [32–34]. For instance, the study by Smerud et al. [35] showed no benefit of ibandronate on LS BMD evolution after KTx, but did demonstrate a modest increase in hip and radius BMD.

In our study, over a follow-up period of 8.9 years, 13.6% of patients experienced a MOF, a rate slightly higher than those typically reported in the literature [36]. Our study is not sufficiently powered to establish a significant link between 2yT BMD modifications and fracture risk. Studies have demonstrated with ECSW a significant reduction of fracture incidence [17] and other did not demonstrate a correlation between cumulative CS doses on fracture occurrence [9]. This discrepancy might be due to differences in population demographics, follow-up duration, fracture risk management strategies and a lack of statistical power. The absence of a significant association between fracture risk and CS withdrawal or cumulative dose suggests that other factors may contribute to fracture outcomes.

While this'real-life'study provides valuable insights, certain limitations should be acknowledged. The retrospective design introduces inherent biases, and the relatively modest sample size may limit the generalizability of the findings. A large number of patients were excluded from the study window, primarily due to the requirement for the DXA to

be performed within 65 days post-transplantation to minimize early post-transplant changes. Additionally, the lack of documentation on CS use prior to KTx and the inconsistent use of other calcium- and phosphate-based medications, which could influence the results, represent further limitations. Moreover, the study did not account for some potential confounding factors, such as patient adherence to medications and lifestyle factors, which could influence bone health outcomes.

In conclusion, our findings show that withdrawing CS therapy can significantly improve BMD, particularly at key bone sites, while continued use leads to further deterioration, suggesting the importance of CS weaning in selected patients. This highlights the complex relationship between CS withdrawal, BMD changes, and fracture risk in KTRs. Further research is warranted to comprehensively understand and better prevent fracture risk in this population.

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Authors' contribution AB, ME, OM, LW, PD conceptualized and supervised the study. AB, ME, OM, LW, PD conducted the experiments and collected data. AB, ME, LS performed the statistical analyses. AB, ME, OM, LS, LW, PD drafted the initial manuscript, while all authors contributed to manuscript revision and approved the final version. Conceptualization—AB, ME, OM, LW, PD Methodology—AB, ME, OM, LW, PD Investigation—AB, ME, OM, LW, PD Data Analysis—AB, ME, OM, LS, LW, PD Writing—Original Draft—AB, ME, OM, LS, LW, PD Writing—Review and Editing—AB, ME, OM, LS, J-FK, J-Y R, EC, CR, FJ, LW, PD Validation—AB, ME, OM, LS, J-F K, J-Y R, EC, CR, FJ, LW, PD.

Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Human and animal rights The authors declare that all procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not include any data involving animals.

Informed consent Informed consent was obtained from all individual participants included in the study.

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