Recovery of Hyperphosphatoninism and Renal Phosphorus Wasting One Year after Successful Renal Transplantation

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Background and objectives: In the first months after successful kidney transplantation, hypophosphatemia and renal phosphorus wasting are common and related to inappropriately high parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF-23) levels. Little is known about the long-term natural history of renal phosphorus homeostasis in renal transplant recipients.

Design, setting, participants: We prospectively followed parameters of mineral metabolism (including full-length PTH and FGF-23) in 50 renal transplant recipients at the time of transplantation (Tx), at month 3 (M3) and at month 12 (M12). Transplant recipients were (1:1) matched for estimated GFR with chronic kidney disease (CKD) patients.

Results: FGF-23 levels (Tx: 2816 [641 to 10665] *versus* M3: 73 [43 to 111] *versus* M12: 56 [34 to 78] ng/L, median [interquartile range]) and fractional phosphorus excretion (FE_{phos}; M3: 45 ± 19% *versus* M12: 37 ± 13%) significantly declined over time after renal transplantation. Levels 1 yr after transplantation were similar to those in CKD patients (FGF-23: 47 [34 to 77] ng/L; FE_{phos} 35 ± 16%). Calcium (9.1 ± 0.5 *versus* 8.9 ± 0.3 mg/dl) and PTH (27.2 [17.0 to 46.0] *versus* 17.5 [11.7 to 24.4] ng/L) levels were significantly higher, whereas phosphorus (3.0 ± 0.6 *versus* 3.3 ± 0.6 mg/dl) levels were significantly lower 1 yr after renal transplantation as compared with CKD patients.

Conclusions: Data indicate that hyperphosphatoninism and renal phosphorus wasting regress by 1 yr after successful renal transplantation.

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Hypophosphatemia is a common complication after successful renal transplantation, occurring in up to 90% of patients in the early posttransplant period (1,2). Persistence of inappropriately high serum levels of fibroblast growth factor-23 (FGF-23), a recently discovered phosphaturic hormone, plays an important role in the pathogenesis of this complication (3,4).

Controversy exists as to whether the renal phosphorus wasting persists on the long term. Most studies suggest a gradual improvement and eventually normalization of serum phosphorus concentrations by 1 yr after renal transplantation. However, skeletal mobilization of phosphorus may oppose persistent renal phosphorus losses. As a result, ongoing phosphorus wasting may be present despite normalization of serum phosphorus. This might contribute to the progressive decline of bone mineral density and increased fracture risk in renal transplant recipients (5,6).

The complexity of renal phosphorus homeostasis in chronic kidney disease (CKD) is well recognized (7). Recent clinical studies demonstrate a high fractional phosphorus excretion in patients with early-stage CKD despite the presence of normophosphatemia (8–10). These findings indicate that in progressive renal failure compensatory increases in renal phosphorus excretion are recruited before the development of hyperphosphatemia. This increase in renal phosphorus excretion is driven, at least partly, by parathyroid hormone (PTH) and by FGF-23 (9,11–13). Renal transplant recipients (RTR) represent a unique subset of patients with CKD. Most of these patient have stage 2 or 3 CKD, based on the National Kidney Foundation CKD classification, even immediately posttransplantation (14).

We aimed to determine the natural history of renal phosphorus handling after successful renal transplantation and to compare renal phosphorus handling between RTR and CKD patients. We prospectively followed parameters of phosphorus metabolism in an unselected cohort of RTR up to 12 mo after successful renal transplantation and compared these with parameters obtained in a cohort of not transplanted CKD patients matched for GFR. The present prospective study extends data from a previous report, describing the short-term natural history of mineral metabolism after successful renal transplantation (15).

Materials and Methods

Study Design and Population

The study presented here consisted of a prospective observational and a case-controlled substudy.

All recipients of a single kidney, transplanted at the University Hospitals Leuven, who consented to participate in our protocol biopsy program were eligible for inclusion in the prospective observational substudy. However, for the analysis presented here only patients with

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an estimated GFR (eGFR) exceeding 30 ml/min at month 12 posttransplantation ($n = 50$) were selected. For the case-controlled substudy, eGFR-matched controls (1:1) were recruited in a blinded fashion from a cohort of nontransplanted CKD patients. These CKD patients were followed at the nephrology outpatient clinic, University Hospital Gasthuisberg, Leuven and have been recruited in the frame of an ongoing epidemiologic trial (clinical trials registry NCT00441623). The distribution of patients over both seasons (winter-summer) was similar in both RTR and CKD patients. The study adhered to the principles of the Declaration of Helsinki and was approved by the ethical committee of the Catholic University of Leuven. All patients provided informed consent.

Procedures, Assays, and Calculations

In RTR, serum samples were collected immediately before transplantation [pre] (random, nonfasting) and at month 3 (M3) and 12 (M12) posttransplantation [post] (fasting). In CKD patients, serum samples were collected during a routine follow-up outpatient visit (random, nonfasting). Samples were stored for <2 h at 5°C until centrifugation. Upon arrival at the laboratory, the blood samples were centrifuged at 3000 rpm for 10 min, aliquotted, and stored at −80°C until analysis. Twenty-four hour urine samples were collected, shaken, aliquotted, and stored at −80°C until analysis.

Serum full-length FGF-23 levels were determined with a sandwich ELISA using two kinds of monoclonal antibodies requiring the simultaneous presence of both the N-terminal and C-terminal portions of FGF-23 (Kainos Laboratories, Inc., Tokyo, Japan). This assay differs from the C-terminal assay (Immunotopics, USA), which recognizes both full-length and processed C-terminal fragments of FGF-23 (16). FGF-23 levels determined in healthy controls ($n = 58$) with the full-length FGF-23 assay amounted to 26.3 ± 0.82 ng/L (13). Serum calcitriol and 25(OH)D3 (calcidiol) levels were measured using a RIA (17,18). Serum concentrations of PTH were determined by an immunoradiometric assay (IRMA), as described elsewhere (19). In contrast to most other commercially available IRMAs for PTH, this assay detects full-length human PTH but not N-terminal truncated fragments, and thereby resembles recently introduced third-generation PTH IRMAs (biointact PTH or whole PTH). This also explains its lower normal range of 3 to 40 pg/ml [ng/L]. A comparison with the PTH 1-to 84-assay from Scantibodies Inc. in a large cohort of hemodialysis patients ($n = 98$) showed a good correlation ($R^2 = 0.92$, $y = 0.91x$). Specific guidelines on the target range of PTH in RTR are currently lacking. Applying current Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines for bone metabolism and disease in CKD (20) and assuming a conversion factor of 2 between intact and biointact PTH (21), target ranges for PTH were defined as follows: CKD stage 1 and 2: 3 to 40 pg/ml; CKD stage 3: 20 to 40 pg/ml. Serum creatinine; (ionized) calcium; phosphorus; immunosuppressive drug trough levels; and urine creatinine, calcium, and phosphorus were measured using standard assays. Measured serum calcium levels were adjusted to albumin levels using the following equation (20):

$$Ca_c = Ca + [(4.0 - Alb(g/dl)) \cdot 0.8]$$

The eGFR was calculated using the Cockcroft and Gault equation and the short Modification of Diet in Renal Disease formula (22). Measures of renal phosphorus handling included the fractional excretion of phosphorus (FE_{phos}, normal range 0 to 25% and the tubular maximum reabsorption of phosphorus corrected for GFR (TmP/GFR, normal range 2.8 to 4.2 mg/dl) (23).

Statistics

Parametric and nonparametric parameters are expressed as mean ± SD and median [interquartile range], respectively. Differences between periods are analyzed using a paired ANOVA or McNemar's test, for continuous and dichotomous variables, respectively. Differences between groups are analyzed using the Wilcoxon rank sum test. Simple linear regression analyses were used to examine the associations between calcidiol, calcitriol, phosphorus, calcium, PTH, FGF-23, creatinine, FE_{PO4}, and eGFR. Nonparametric distributed variables, including PTH and FGF-23, were ln-transformed for the regression analyses. Multivariate linear regression analysis was performed including all univariately associated variables ($P < 0.2$). After excluding collinearity, the best subset of variables was selected by backward elimination on $P < 0.2$. This subset was then subjected to a final backward elimination procedure on $P < 0.05$. Inspection of residual plots assured that the *a priori* assumptions for linear regression were justified. The SAS version 9.1 (SAS Institute, Cary, NC) software program was used for the statistical analysis. Two-sided $P < 0.05$ was considered statistically significant. In addition to *P*-values, we report *t* scores for individual parameters from the linear regression models to quantify the strength of associations.

Results

Patient Characteristics

Demographics and maintenance therapy are summarized in Table 1 and 2. There were no significant differences in age, gender, weight, and length between CKD patients and RTR. The body mass index was slightly higher in the CKD patients. Primary renal diagnosis was missing in a larger proportion of CKD patients. Maintenance immunosuppression at M3 posttransplantation consisted of corticosteroids (98%), a calcineurin inhibitor (tacrolimus, 94% or cyclosporine, 4%), and an antimetabolite (mycophenolate mofetil, 84% or malononitrilamide, 2%). Intravenous methylprednisolone was administered at the dose of 500 mg on the day of transplantation and 40 mg at the first postoperative day. Subsequently, methylprednisolone was started at the dose of 16 mg orally and tapered to 10 mg orally during the second month, 6 mg orally during the third month, and 4 mg orally thereafter. In 13 patients therapy with steroids was halted between M3 and M12. Cyclosporine and tacrolimus dosing was concentration controlled according to standard protocols. Mycophenolate mofetil dosage was adjusted in case of intolerance. Acute allograft rejection occurred in 12 patients. All rejection episodes were successfully treated with corticosteroid pulse therapy.

There were no significant differences in the usage of phosphate binders. More RTR were on active vitamin D therapy at M12. There was no current or past calcimimetic use in any of the patients. Five RTR had a history of parathyroidectomy before transplantation.

The mean eGFR (Modification of Diet in Renal Disease) in RTR amounted to 46.5 ± 11.8 and 52.8 ± 11.5 ml/min/1.73m^2, at M3 and M12 respectively. Renal function was almost identical in the CKD counterparts.

Natural History of Mineral Metabolism in RTR

Table 3 shows the natural history of parameters of mineral metabolism after successful renal transplantation. As reported

Table 1. Demographics[a]

Variable	CKD ($n = 50$)	RTR ($n = 50$)	*P*
Time on dialysis (m)	-	32.7 [19.6-50.8]	
Age	57.7 ± 11.0	52.0 ± 14.4	0.06
Sex (% male/female)	60/40	62/38	0.84
Donor type (deceased/living related)	-	47/3	-
Weight (kg)	79.5 ± 17.6	72.6 ± 13.7	0.07
Length (m)	1.70 ± 0.09	1.70 ± 0.09	0.85
Body mass index (kg/l^2)	27.1 ± 5.1	24.9 ± 4.4	0.04
Renal diagnosis [n (%)]			0.04
Diabetic nephropathy	3 (6)	5 (10)	
Glomerulonephritis/vasculitis	21 (42)	16 (32)	
Interstitial nephritis	2 (4)	4 (8)	
Hypertensive/large vessel disease	0 (0)	3 (6)	
Cystic/heriditary/congenital diseases	7 (14)	12 (24)	
Miscellaneous	0 (0)	3 (6)	
Etiology unknown or missing	17 (34)	7 (14)	

[a]CKD, chronic kidney disease; RTR, renal transplant recipient.

Table 2. Drug regimen[a]

Variable	CKD ($n = 50$)	RTR ($n = 50$)		*P*, CKD *versus* RTR	
		3M	12M	3M	12M
Immunosuppression (*n*)					
corticosteroids	4	49	36	<0.0001	<0.0001
calcineurin inhibitor	2	49	49	<0.0001	<0.0001
antimetabolite	1	43	41	<0.0001	<0.0001
Mineral metabolism (*n*)					
phosphate binder	5	2	3	0.24	0.46
active vitamin D	0	2	6	0.15	0.01
naive vitamin D	2	2	1	1.0	0.56
Other (*n*)					
diuretics	10	6	6	0.28	0.28

[a]3M, month 3; 12M, month 12.

previously, calcidiol, PTH, and especially FGF-23 showed a dramatic decrease, whereas calcitriol levels almost doubled within the first 3 mo after successful renal transplantation (4). These changes were accompanied by a significant increase of serum calcium levels and a drop of serum phosphorus levels. After M3, serum levels of FGF-23, PTH, and calcitriol showed changes in the same direction, but at a much slower pace. FGF-23 decreased by 23.1% [-50.7 to 12.9%] ($P < 0.01$), PTH decreased by 26.0% [−61.0 to 16.6%] ($P < 0.01$) and calcitriol increased by 5.7% [−11.8 to 46.6%] (P = NS). Elevated FGF-23 levels (>50 ng/L) were observed in 66 and 57% of the RTR at M3 and M12, respectively. PTH levels above Kidney Disease Outcomes Quality Initiative targets were observed in 40 and 32% of the RTR at M3 and m12, respectively. Calcidiol levels, conversely, slightly increased between M3 and M12 (13.9% [−25.7 to 73.2]) ($P = 0.07$). Calcidiol stores were sufficient (>30 ng/ml) in most patients (55%) at the time of transplantation. At M3 and M12, conversely, 68 and 56% of the patients demonstrated calcidiol insufficiency (10 to 30 ng/ml). Severe deficiency (<10 ng/ml) was present in another 8 and 6%, respectively. Serum phosphorus and calcium levels returned to the normal range in most the patients after M3. Mild-to-moderate hypophosphatemia, defined as a serum phosphorus level ≤2.3 mg/dl was observed in 32 and 14% of the patients at M3 and M12, respectively. FE_{phos} decreased over time (45 ± 19% *versus* 37 ± 14%, M3 *versus* M12, $P = 0.01$)

Mineral Metabolism in RTR and CKD Patients, Matched for eGFR

Compared with CKD patients, RTR at M3 had significantly lower serum levels of phosphorus and calcidiol, and significantly higher serum levels of calcium, FGF-23 and PTH. At M12, differences were less pronounced and significance was lost for calcidiol and FGF-23. Calcitriol levels did not differ

Table 3. Parameters of mineral metabolism in RTR and patients with chronic kidney disease[a]

Parameter	RTR			CKD			
	TX	3M	12M	3M *versus* 12M		CKD *versus* 3M	CKD *versus* 12M
Phosphate (mg/dl)	5.0 ± 1.3	2.6 ± 0.6	3.0 ± 0.6	0.0005	3.3 ± 0.6	<0.0001	0.01
Hypophosphatemia (<2.3 mg/dl) (%)	0	32	14	0.0004	4	0.0003	0.08
Calcium (mg/dl)	9.7 ± 0.8	10.0 ± 0.7	9.5 ± 0.6	<0.0001	9.4 ± 0.3	<0.0001	0.4
Albumine (g/L)	44.0 ± 4.7	43.4 ± 3.0	44.3 ± 2.4	0.07	45.7 ± 3.0	0.0002	0.004
Bicarbonate (mmol/L)	-	22.7 ± 2.3	22.9 ± 2.6	0.8	25.2 ± 3.0	<0.0001	<0.0001
Ca_c (mg/dl)	9.3 ± 0.7	9.7 ± 0.7	9.1 ± 0.5	<0.0001	8.9 ± 0.3	<0.0001	0.02
Hypercalcemia (>10.2 mg/dl) (%)	9	22	2	<0.0001	0	0.0005	0.32
Calcidiol (μg/L)	33.6 ± 16.7	23.6 ± 11.0	27.3 ± 14.5	0.07	29.1 ± 14.3	<0.05	0.42
Sufficient (≥30)/insufficient (10 to 30)/deficient (<10) (%)	55/41/4	24/68/8	38/56/6	0.32	46/46/8	0.06	0.6
Calcitriol (ng/L)	21.4 [15.2 to 27.1]	38.3 [30.9 to 50.0]	46.8 [35.3 to 57.6]	0.93	41.2 [33.9 to 51.9]	0.48	0.17
Deficiency (<20) (%)	55	10	0	<0.0001	8	0.72	0.60
PTH (ng/L)	112.5 [66.1 to 233.5]	35.9 [23.3 to 68.7]	27.2 [17.0 to 46.0]	0.008	17.5 [11.7 to 24.4]	<0.0001	0.003
PTH above K/DOQI targets (%)	40	40	32	0.06	10	0.0005	0.007
FGF-23 (ng/L)	2816 [641 to 10,665]	73 [43 to 111]	56 [34 to 78]	0.008	47 [34 to 77]	0.02	0.60
FGF-23 >50 ng/L (%)	100	66	57	0.10	45	0.04	0.57
Total alkaline phosphatases (IU/L)	200 [160 to 286]	169 [146 to 211]	176 [146 to 230]	0.94	183 [155 to 222]	0.27	0.58
Creatinine (mg/dl)	7.63 ± 2.39	1.59 ± 0.35	1.41 ± 0.27	<0.0001	1.49 ± 0.43	0.12	0.40
eGFR ml/min/1.73m² (Cockroft and Gault)	-	51.3 ± 13.2	56.6 ± 13.7	0.01	54.4 ± 15.5	0.40	0.40
eGFR ml/min/1.73m² (MDRD)	-	46.5 ± 11.8	52.8 ± 11.5	<0.0001	50.8 ± 15.7	0.18	0.41
K/DOQI stage 2/3 (%)	-	32/68	42/58	0.27	44/56	0.22	0.33
CrCl ml/min/1.73m²	-	50.2 ± 26.9	54.3 ± 21.0	0.19	50.4 ± 19.3	0.55	0.23
Phosphaturia (mg/d)	-	727 [541 to 977]	872 [570 to 1025]	0.53	790 [570 to 1089]	0.87	0.71
FE_{phos} (%)	-	45 ± 19	37 ± 13	0.01	35 ± 16	0.007	0.25
TmP/GFR (mg/dl)	-	1.52 ± 0.76	1.94 ± 1.52	0.0006	2.18 ± 0.72	<0.0001	0.17

Data are represented as mean ± SD or median [interquartile range]. [a]CKD, chronic kidney disease; PTH, parathyroid hormone; FGF-23, fibroblast growth factor-23; eGFR, estimated GFR, MDRD, Modification of Diet in Renal Disease; K/DQQI, Kidney Disease Outcomes Quality Initiative; CrCl, creatinine clearance; FE_{phos}, fractional phosphorus excretion; TmP/GFR, tubular maximum reabsorption of phosphorus corrected for GFR; Ca_c, albumin corrected calcium concentration.

between the two groups at any of the two time points. FE_{phos} was significantly higher in RTR as compared with their CKD counterparts at M3 only (Table 3).

Regulators of Serum Levels of FGF-23 in RTR

Table 4 demonstrates factors associated with FGF-23 at M3 and M12. At M3, higher FGF-23_{pre}, albumin-corrected calcium, PTH, and lower calcitriol were each significantly associated with higher FGF-23. On the basis of regression *t* scores, FGF-23_{pre} was the strongest univariate predictor. In the multivariate model, FGF-23_{pre}, calcitriol, PTH and albumin-corrected calcium were found to be independently associated with FGF-23. These variables explain 65% of the variation of FGF-23 at M3 ($P < 0.0001$). At M12, higher FGF-23_{pre} and albumin-corrected calcium, and lower calcitriol and eGFR, were each significantly associated with higher FGF-23 ($P < 0.05$ for each); on the basis of the regression *t* scores, eGFR was the strongest univariate predictor. In the multivariate model, FGF-23_{pre} and eGFR were found to be independently associated with FGF-23. These variables explain 37% of the variation of FGF-23 at M12 ($P < 0.0001$).

Regulators of Serum Levels of PTH in RTR

Table 5 demonstrates factors associated with PTH at M3 and M12. At M3, higher PTH_{pre}, albumin-corrected calcium and FGF-23, and lower eGFR were each significantly associated with higher PTH; on the basis of regression *t* scores, PTH_{pre} was the strongest univariate predictor. In the multivariate model, PTH_{pre}, FGF-23, and eGFR were independently associated with FGF-23. These variables explain 47% of the variation of PTH at M3 ($P < 0.0001$). At M12, only higher PTH_{pre} was significantly associated with higher PTH ($R^2 = 0.09$, $P < 0.05$).

Regulators of Serum Levels of Calcitriol in RTR

Table 6 demonstrates factors associated with calcitriol at M3 and M12. At M3, lower FGF-23 and higher alkaline phosphatases were each significantly associated with higher calcitriol; on the basis of regression *t* scores, alkaline phosphatases were the strongest univariate predictor. In the multivariate model, lower FGF-23 and higher PTH were independently associated with higher calcitriol. These variables explain 26% of the variation of calcitriol at M3 ($P < 0.001$). At M12, only lower FGF-23 was found to be associated with higher calcitriol ($R^2 = 0.19$, $P = 0.004$)

Discussion

To get a better insight in posttransplant phosphorus homeostasis, we prospectively followed blood and urinary parameters of phosphorus metabolism up to 12 mo after successful renal transplantation and compared these with parameters obtained in a cohort of CKD patients matched for GFR. The major finding of the study presented here was that hyperphosphatoninism and renal phosphorus wasting regress by 1 yr after successful renal transplantation.

Despite a tremendous decrease posttransplantation, FGF-23 levels at M3 remained significantly higher in RTR as compared with CKD patients matched for eGFR. This observation strengthens the notion of inappropriate hyperphosphatoninism in the early posttransplant period as put forward in previous reports (3,4). After M3, however, FGF-23 levels showed a further decline to reach concentrations at M12 that were similar to those of CKD counterparts. Apparently, inappropriate hyperphosphatoninism fades away by 1 yr after successful transplantation. As in CKD patients (9,13,24), renal function was a major determinant of FGF-23 serum levels in RTR at M12.

Table 4. Factors associated with FGF-23: univariate and multivariate regression analyses using FGF-23 as the dependent variable

Independent Variables	M3			M12		
	β coefficient	*P*	R^2	β coefficient	*P*	R^2
Univariate models						
FGF-23_{pre}	0.28	<0.0001	0.42	0.16	0.003	0.19
Albumin-corrected calcium	0.5	0.002	0.19	0.43	0.02	0.11
PTH	0.35	0.007	0.14	0.17	0.07	0.07
Calcitriol	−0.011	0.03	0.11	−0.018	0.004	0.19
eGFR	−0.026	0.007	0.14	−0.027	0.0006	0.23
Multivariate						
FGF-23_{pre}	0.23	<0.0001		0.14	0.003	
Calcitriol	−0.01	0.003		-	-	
PTH	0.27	0.008		-	-	
Albumin-corrected calcium	0.29	0.015		-	-	
eGFR	-	-		−0.025	0.0008	
Overall model		<0.0001	0.65		<0.0001	0.37

Parameters included in the model: FGF-23_{pre}, serum albumin-corrected calcium, phosphorus, PTH, calcidiol, calcitriol alkaline phosphatases, and eGFR. PTH and FGF-23 were Ln-transformed for regression analyses. Only parameters univariately associated at $P \leq 0.2$ for at least one time point are mentioned in the table.

Table 5. Factors associated with PTH: univariate and multivariate regression analyses using PTH as the dependent variable

Independent Variables	M3			M12		
	β coefficient	*P*	R^2	β coefficient	*P*	R^2
Univariate models						
PTH_{pre}	0.44	<0.0001	0.28	0.37	0.04	0.09
Phosphorus	−0.38	0.09	0.06	−0.33	0.26	0.03
Albumin-corrected calcium	0.5	0.004	0.16	0.49	0.18	0.04
FGF-23	0.4	0.007	0.14	0.39	0.07	0.07
Calcitriol	0.009	0.1	0.06	0.0014	0.92	0
eGFR	−0.022	0.03	0.09	−0.02	0.18	0.04
Multivariate						
PTH_{pre}	0.45	<0.0001		0.37	0.04	
FGF-23	0.30	0.02		-	-	
eGFR	−0.02	0.04		-	-	
Overall model		<0.0001	0.47		0.04	0.09

Parameters included in the model: $FGF\text{-}23_{pre}$, serum albumin-corrected calcium, phosphorus, PTH_{pre}, calcidiol, calcitriol alkaline phosphatases, and eGFR. PTH and FGF-23 were Ln-transformed for regression analyses. Only parameters univariately associated at $P \leq 0.2$ for at least one time point are mentioned in the table.

Table 6. Factors associated with calcitriol: univariate and multivariate regression analyses using calcitriol as the dependent variable

Independent Variables	M3			M12		
	β coefficient	*P*	R^2	β coefficient	*P*	R^2
Univariate models						
PTH	6.53	0.097	0.06	0.2	0.92	0
FGF-23	−9.45	0.023	0.11	−10.6	0.004	0.19
Calcidiol	0.04	0.89	0	0.22	0.18	0.04
Alkaline phosphatases	0.086	0.006	0.15	0.023	0.53	0.01
eGFR	0.26	0.35	0.02	0.56	0.006	0.17
Multivariate						
PTH	11.54	0.0034		-	-	-
FGF-23	−14.1	0.0009		−10.6	0.004	0.19
Overall model		0.001	0.26			

Parameters included in the model: serum albumin-corrected calcium, phosphorus, PTH, FGF-23, calcidiol, calcitriol alkaline phosphatases, and eGFR. PTH and FGF-23 were Ln-transformed for regression analyses. Only parameters univariately associated at $P \leq 0.2$ for at least one time point are mentioned in the table.

Contrary to serum FGF-23 levels and despite an important drop early after transplantation, serum PTH levels remained significantly higher 1 yr after renal transplantation as compared with their CKD counterparts. Applying CKD guidelines, 32% of patients had a PTH level above target one year after transplantation. The long lifespan of parathyroid cells (approximately 20 yr) with a cell renewal rate of approximately 5% per year (25) contributes to the very slow involution of the gland after renal transplantation. In addition to PTH_{pre}, FGF-23 was found to be independently associated with PTH both 3 and 12 mo after transplantation. This finding and the observation that PTH levels are elevated in hypophosphatemic disorders caused by elevated FGF-23 levels (26) support the hypothesis that FGF-23 is involved in the pathogenesis of hyperparathyroidism. This hypothesis is further corroborated by the observation in dialysis patients that elevated circulating FGF-23 levels directly correlate with PTH levels and predict refractory hyperparathyroidism (27). On the other hand, there is also some evidence that PTH may increase FGF-23 levels (28,29). Additional studies are required to elucidate this complex relationship.

Along with the changes in serum concentration of the phosphaturic hormones FGF-23 and PTH, the fractional urinary excretion of phosphorus in RTR decreased toward values similar to those observed in CKD patients with a comparable degree of renal impairment. This observation questions the thesis that calcineurin inhibitor therapy contributes substan-

tially to renal phosphorus wasting in the first year after transplantation, as advanced by others (30,31). Our data also suggest that the role of renal phosphorus wasting in the pathogenesis of posttransplant bone mineral density losses declines with time after transplantation.

Serum bicarbonate levels were significantly lower in RTR as compared with CKD patients. The effect of a disturbed acid-base homeostasis on bone mineral metabolism is an issue of ongoing controversy that requires further research (32).

It should be of note that we cannot exclude the possibility of persisting phosphorus wasting in a subset of patients. Larger studies with longer follow-up are required to delineate the magnitude and consequences of this complication more precisely.

Despite the observation of similar renal phosphorus handling, serum phosphorus levels in RTR at 1 yr after transplantation remained significantly lower as compared with CKD patients. Balance studies are needed to puzzle out whether this is due to differences in dietary habits, gastrointestinal absorption, and/or bone release.

Calcitriol levels showed a rapid and marked increase after transplantation. Levels at M3 and M12 were similar to those observed in the CKD counterparts. None of the RTR had serum calcitriol <20 ng/L, *i.e.,* calcitriol deficiency, at M12. As reported previously, lower FGF-23 and higher PTH levels were associated with higher calcitriol levels at M3. This observation is in line with the opposing actions of FGF-23 and PTH in the regulation of 25-hydroxyvitamin D-1α-hydroxylase. At M12, only renal transplant function was found to be associated with calcitriol levels. Opposite to calcitriol, calcidiol levels decreased significantly during the first 3 mo after successful renal transplantation. Thereafter, calcidiol levels showed a modest increase. Nonetheless, vitamin D insufficiency, defined as serum calcidiol level <30 μg/L, was still present in 62% of the patients 1 yr after transplantation. This figure was slightly higher than what was observed in the CKD counterparts. Given this high prevalence of vitamin D insufficiency, the many pleiotropic effects of native vitamin D (33), and the association of vitamin D deficiency with incident cardiovascular disease (34), a more liberal vitamin D supplementation policy should be considered in CKD patients as well as in RTR. Meanwhile, additional prospective and interventional studies should be initiated to definitely proof the benefits of this policy.

An aspect of this study that could be seen both as a limitation as well as a strength is that it was conducted in the course of routine patient care and therefore, represents "real life" medical care. Further strengths include the prospective design with 12-mo follow-up of all RTR and the inclusion of control population of CKD patients, matched for eGFR.

In conclusion, our data indicate that hyperphosphatoninism and renal phosphorus wasting regress by 1 yr after successful renal transplantation. Pretransplant serum levels of FGF-23 and PTH predict posttransplant serum levels independent of renal function up to 1 yr after engraftment.

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Disclosures

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