PHOSPHATE METABOLISM DISTURBANCES IN KIDNEY TRANSPLANT RECIPIENTS

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Introduction

Mineral metabolism disorders are present in many kidney transplant recipients. The aim of the study was to evaluate phosphate metabolism disturbances in kidney recipients with good graft function.

Materials and methods

The study comprised 230 kidney transplant recipients (135 male, 95 female), aged 19 - 78 years, with stable renal function and measured creatinine > 50 mL/min. The estimations were made 1-327 months posttransplant (in 44 patients within first 11 posttransplant months, and in 186 patients ≥ 12 months posttransplant).

The following parameters were estimated :
- iPTH, serum, IRMA (IBL, Germany),
- CrossLaps, Cs, serum, β-CrossLaps (Immunoassay, "cobas^{R}" , Roche DiagnosticsGmbH, Germany)
- 25(OH)D_3, serum (Immunoassay, "cobas^{R}" , Roche DiagnosticsGmbH, Germany)
- Bone alkaline phosphatase, bALP, serum: Alkaline phosphatase electrophoresis on agarose gel with lectin; semi-automated hydrasis SEBIA system (France) was used (Hydragel 15 ISO-PAL kits)
- Ca ionized, Cai, whole blood, (ion selective electrode, Gem premier 3000 blood gas analyzer, Instrumentation Laboratories, Chicago, Il, USA)
- Cyclosporine A/ tacrolimus / sirolimus/ everolimus trough levels, 12 hours after last dose, Immunoassay, SIEMENS Dimension ^{R}, Siemens Healthcare Diagnostics Inc
- Ca/ 24-hour urine, Ca_u
- Phosphate/ 24-hour, P_u
- Total alkaline phosphatase, ALP, total Ca, Pi, serum and urine calcium, phosphate, creatinine were determined using standard recommended methods.
- Tubular maximum reabsorption of phosphate per litre of GFR was estimated (TmP/GFR)
- The ratio of the renal calcium clearance to renal creatinine clearance was derived as follows :

Calcium clearance/creatinine clearance= $U_{Ca} \times S_{Cr} / S_{Ca} \times U_{Cr.}$

Immunosuppressive therapy:
cyclosporine A + MMF/ EC-MPS (2 patients),
cyclosporine A + corticosteroids (7 patients)
cyclosporine A + azathioprine + corticosteroids (8 patients),
cyclosporine A + MMF/ EC-MPS + corticosteroids (118 patients),
tacrolimus + corticosteroids (1 patient)
tacrolimus + MMF/ EC-MPS ((1 patient)
tacrolimus + MMF/ EC-MPS + corticosteroids (76 patients)
sirolimus + MMF/ EC-MPS + corticosteroids (4 patients)
sirolimus + MMF/ EC-MPS (2 patients)
everolimus + MMF/ EC-MPS + corticosteroids (8 patients)
everolimus + MMF/ EC-MPS (2 patients)
azathioprine + corticosteroids (2 patients)

Statistical analysis

The data were presented as median values with interquartile range.
Correlations were estimated using Spearman's rank correlation test.
The differences between groups were tested using Mann-Whitney U test.
P values <0.05 were considered statistically significant.

Results

Blood was drawn in the morning after an overnight fast, and separated sera were analyzed immediately, or frozen until the assay performance. Ca^{++} was estimated in whole blood. No patient had a rejection episode during sample collection and testing, and none received calcitriol, paricalcitol, calcimimetics or bisphosphonates. No patient showed signs of liver disease (serum transam

Table 1A
Descriptive statistics, patient characteristics

Parameter	N	Median	Lower quartile	Upper quartile
Age, years	230	53	43	61
Time spent on dialysis, months	217*	42	23	72
Posttransplant period duration, months	230	26	12	56
Creatinine (serum), μmol/L	230	121.5	103	142
Creatinine clearance, mL/min	230	68.15	60.5	80.8
Cyclosporine A, total daily dose, mg	136	125	100	150
Cyclosporine A, total daily dose, mg/kg BW	136	1.705	1.39	2.13
Cyclosporine A, trough level, ug/L	136	102.5	89	118.5
Tacrolimus, total daily dose, mg	78	3.0	2	5
Tacrolimus, total daily dose, mg/kg BW	78	0.0375	0.028	0.064
Tacrolimus, trough level, ug/L	78	6	4.4	7.6

*The data for patients who had a second graft were excluded

Table 1B
Descriptive statistics, blood/ urine parameters

Parameter	N	Median	Lower quartile	Upper quartile	Reference range
Ca, mmol/L	230	2.47	2.37	2.59	2.14 - 2.53
Ca^{++}, mmol/L	228	1.26	1.21	1.33	1.18 - 1.32
Ca/24- hour urine, mmol/dU	230	4.12	2.66	6.36	2.5 - 7.5
Calcium : creatinine clearance ratios	230	0.016	0.01	0.024	0.01 - 0.02
Pi, mmol/L	230	0.90	0.80	1.08	0.79 - 1.42*
Phosphate / 24- hour urine,mmol/dU	230	26.445	19.54	33.28	12.9 - 42
TmP/GFR, mmol/L	230 135(M) 95(F)	0.675 0.62 0.78	0.54 0.52 0.58	0.81 0.74 0.92	** M 0.90 - 1.35, F 0.88 -1.42
iPTH, pmol/L	230	9.95	6.5	13.9	1.0 - 6.0
25(OH)D_3 ,nmol/L	223	46	31	66	>75, < 75 deficiency
ALP, U/L	230	71.5	59	90	M 60 - 142, F 54 -119, F >50 years 64 - 153
BALP, U/L	217	39	29	53	M 15-41.3, F premenopausal 11.6-29.6, F postmenopausal 14.2-42.7
CrossLaps, μg/L	230	0.569	0.419	0.836	M 30-50 years < 0.584, 50-70 years < 0.704, >70 years < 0.85, F premenopausal < 0.633 F postmenopausal < 1.008

* Pi < reference range in 49/230 patients, ** TmP < reference range in 187/230 patients

Significant differences:
In patients in whom the estimations were made within first 11 posttransplant months (N=44), Pi (0.825, 0.74 –1.005 mmol/L) and TmP (0.61, 0.485-0.765, mmol/L) were significantly lower than in those in whom the estimations were performed ≥ 12 months posttransplant (N=186, Pi 0.91, 0.82-1.08 mmol/L, TmP 0.69, 0.55-0.82 mmol/L). P; Pi <0.05, TmP <0.05 (Mann-Whitney U test).
In patients in whom the estimations were made within first 11 posttransplant months, serum total and ionized calcium, PTH, total and bone alkaline phosphatase, cyclosporine daily dose (mg/kg), cyclosporine trough level, tacrolimus daily dose (mg), tacrolimus trough level were significantly higher, and 25(OH)D_3 and serum creatinine significantly lower than in those in whom the estimations were performed ≥ 12 months posttransplant.
In men (N=135), Pi (0.87, 0.78-0.96 mmol/L) and TmP (0.62, 0.52-0.74, reference range 0.90-1.36 mmol/L) were significantly lower than in women (N=95, Pi 1.03, 0.84-1.13 mmol/L, TmP 0.78, 0.58-0.92, reference range 0.88-1.42 mmol/L). P; Pi <0.00001, TmP <0.0000….
Ionized calcium was significantly lower and cyclosporine ((mg(kg) and tacrolimus (mg) daily doses were significantly higher in women than in men.
In premenopausal women, Pi (N= 39, 0.89, 0.8-1.09 mmol/L) and TmP (0.71, 0.54-0.86) were significantly lower than in postmenopausal ones (N=56, Pi 1.06, 0.915-1.16 mmol/L, TmP 0.845, 0705-0.94 mmol/L). P; Pi <0.01, TmP <0.05
Total and bone alkaline phosphatase and crosslaps were significantly higher in postmenopausal than premenopausal women. Cyclosporine (mg/kg) and tacrolimus (mg, mg/kg) daily doses were higher in premenopausal than postmenopausal women

Table 2
Statistically significant correlations, all subjects

Pi : Ca	R = -0.27	p< 0.00005	N = 230
Pi : Ca^{++}	R = -0.41	p< 0.00000..	N = 228
Pi : Ca:Cr clearance ratio	R = -0.16	p< 0.05	N = 230
Pi : serum creatinine	R = -0.14	p< 0.05	N = 230
Pi : iPTH	R = -0.34	p< 0.00000..	N = 230
Pi : ALP	R = -0.17	p< 0.05	N = 230
Pi : tacrolimus trough level	R = -0.27	p< 0.05	N = 78
Pi : creatinine clearance	R = 0.18	p< 0.01	N = 230
Pi : Cyclosporine A, trough level	R = 0.19	p< 0.05	N = 136
TmP/GFR : Ca	R = -0.28	p< 0.00005	N = 230
TmP/GFR : Ca^{++}	R = -0.40	p< 0.00000	N = 228
TmP/GFR : Ca:Cr clearance ratio	R = -0.22	p< 0.001	N = 230
TmP/GFR : iPTH	R = -0.33	p< 0.0000…	N = 230
TmP/GFR : ALP	R = -0.17	p< 0.05	N = 230

IPTH correlated significantly positively with dialysis vintage, total and ionized Ca, Ca:creatinine clearance ratios, total and bone alkaline phosphatase, crosslaps, cyclosporine trough levels, and negatively with posttransplant period duration and 25(OH)D_3.

Multiple regression analysis
Dependent variable, Pi: all patients

Source	Type III Sum of Squares	df	Mean Square	F	P value
Corrected Model	2.073[a]	14	0.148	5.745	<0.001
Intercept	1.288	1	1.288	49.977	<0.001
Age					0.875
Time spent on dialysis					0.494
Posttransplant period duration					0.161
iPTH					<0.001
ALP					0.455
bALP					0.595
crosslaps					0.011
Ca					0.088
Ca^{++}					<0.001
Ca/24- hour urine					0.430
Calcium :creatinine clearance ratios					0.790
25(OH)D_3					0.904
Creatinine (serum)					0.107
Creatinine clearance					0.517
Error	4.717	183	0.026		
Total	176.463	198			
Corrected Total	6.790	197			

a. R Squared =0.305 (Adjusted R Squared = 0.252)

Dependent variable Pi, patients on cyclosporine, N= 136

Source	Type III Sum of Squares	df	Mean Square	F	P value
Corrected Model	1.287[a]	16	0.080	4.226	<0.001
Intercept	0.292	1	0.292	15.359	<0.000
Age					0.911
Time spent on dialysis					0.581
Posttransplant period duration					0.180
IPTH					0.035
ALP					0.730
BALP					0.365
Crosslaps					0.625
Ca					0.539
Ca^{++}					0.016
Ca/24- hour urine					0.017
Calcium : creatinine clearance ratios					0.044
25(OH)D_3					0.064
Creatinine (serum)					0.117
Creatinine clearance					0.009
Cyclosporine A, total daily dose, mg					0.640
Cyclosporine A, trough level					0.040
Error	1.846	97	0.019		
Total	106.056	114			
Corrected Total	3.133	113			

a.R Squared = 0.411 (Adjusted R Squared = 0.314)

Conclusions

- Hypophosphatemia occurs in about 20% of kidney transplant recipients with good and stable graft function, but low tubular phosphate reabsorption is present in the vast majority of them.
- Serum phosphate levels and tubular phosphate reabsorption are related to PTH and sex.
- Cyclosporine and tacrolimus might influence phosphatemia inversely. Further investigations are needed.

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