CALCIUM AND PHOSPHATE URINE EXCRETION IN HYPERCALCEMIC KIDNEY RECIPIENTS

Ružica Šmalcelj

Zagreb University Hospital Center, Department of Internal Medicine, Zagreb, Croatia

Introduction

Most kidney transplant recipients, despite good and stable renal function, have metabolic bone disorder. Hypercalcemia occurs also in these patients.
The aim of the study was to evaluate calcium and phosphate urine excretion in hypercalcemic kidney recipients with good and stable graft function.

Materials and methods

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 (Immunoassay , SIEMENS Dimension R, Siemens Healthcare Diagnostics Inc) / everolimus (QMS Everolimus Immunoassay, Thermo Fischer Scientific) trough levels, 12 hours after last dose,
•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) (1)
•The ratio of renal calcium clearance to renal creatinine clearance was derived as follows (2):
Calcium clearance/creatinine clearance=

$$U_{Ca} \times S_{Cr} / S_{Ca} \times U_{Cr}$$

According to the calcium : creatinine clearance ratios, patients were divided into three groups; 1) < 0.01, as seen in conditions caused by impaired sensitivity of calcium-sensing receptors, 2) 0.01-0.02, normal range, 3) >0.02, usually found in hyperparathyroidism

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 transaminase levels were within the reference range), or was immobilized.

Immunosuppressive therapy:

cyclosporine A + mycophenolate mofetil (1 patient),
cyclosporine A + corticosteroids (1 patient)
cyclosporine A + azathioprine + corticosteroids (3 patients),
cyclosporine A + mycophenolate mofetil + corticosteroids (29 patients),
tacrolimus + mycophenolate mofetil + corticosteroids (11 patients)
sirolimus+ mycophenolate mofetil + corticosteroids (2 patients)
everolimus+ mycophenolate mofetil + corticosteroids (1 patient)

Statistical analysis

The data are presented as median values with range.
Correlations were estimated using Spearman's rank correlation test.
The differences between groups were tested using Kruskal – Wallis (three groups), or Mann-Whitney U test (two groups).
P values <0.05 were considered statistically significant.

Results

Table 1A
Descriptive statistics, patient characteristics

Parameter	N	Median	Min.	Max.
Age, years	48	53.5	19	74
Time spent on dialysis, months	46*	65.5	3.5	148
Posttransplant period duration, months	48	16.5	2	277
Creatinine, µmol/L	48	119.5	61	179
Creatinine clearance, mL/min	48	70.95	52.9	142.2
Cyclosporine A, total daily dose, mg	34	125	87.5	225
Cyclosporine A, total daily dose, mg/kg BW	34	1.86	1.13	3.04
Cyclosporine A, trough level, ug/L	34	105	65	175
Tacrolimus, total daily dose, mg	11	2.5	1.75	11
Tacrolimus, total daily dose, mg/kg BW	11	0.03	0.03	0.16
Tacrolimus, trough level, ug/L	11	7.8	4.2	11.2

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

Table 1B
Descriptive statistics, blood/ urine parameters

Parameter	N	Median	Min.	Max.	Reference range
Ca, mmol/L	48	2.68	2.54	3.27	2.14 – 2.53
Ca^{++}, mmol/L	48	1.37	1.33	1.69	1.18-1.32
Ca/24- hour urine, mmol/dU	48	6.19	0.72	14.97	2.5 – 7.5
Calcium : creatinine clearance ratios	48	0.021	0.003	0.054	0.01-0.02
Pi, mmol/L	48	0.81	0.46	1.19	0.79 – 1.42
Phosphate /24- hour urine, mmol/dU	48	28.445	14.03	43.47	12.9-42.0
TmP/GFR, mmol/L*	48	0.54	0.25	0.96	M 0.90-1.35, F 0.88-1.42
iPTH, pmol/L	48	17.15	2.1	97.6	1.0 – 6.0
25(OH)D_3 ,nmol/L	45	43	9.0	147	>75, < 75 deficiency
ALP, U/L	48	94.5	32	327	M 60- 142, F 54-119, F >50 years 64-153
bALP	45	56.5	24	304	M 15-41.3, F premenopausal 11.6-29.6, F postmenopausal 14.2-42.7
CrossLaps, µg/L	48	0.775	0.22	3.61	M 30-50 years < 0.584, 50-70 years < 0.704, >70 years < 0.85, F premenopausal < 0.633 F postmenopausal < 1.008

**TmP/GFR, mmol/L, inter-quartile range: 0.435-0.685*

Table 2
Renal calcium clearance to creatinine clearance ratios

Ca:Cr clearance ratio	Frequencies
< 0.01 (group 1)	12/48
0.01-0.02 (group 2)	11/48
> 0.02 (group 3)	25/48

The only significant difference between these groups of patients was age, years (median, range), p < 0.05:

Group 1: 42, 26-62
Group 2: 50, 30-62
Group 3: 60, 19-74

Table 3
Statistically significant correlations, all subjects

Age : Ca/24- hour urine	R= 0.34	p< 0.05	N = 48
Age : Ca : Cr clearance ratios	R= 0.464	p< 0.001	N = 48
Dialysis vintage : Ca	R= 0.43	p< 0.005	N = 46
Dialysis vintage : Ca^{++}	R= 0.49	p< 0.0005	N = 46
Dialysis vintage : iPTH	R= 0.37	p< 0.05	N = 46
Posttransplant period duration : bALP	R= -0.47	p< 0.005	N = 45
Posttransplant period duration : Cs	R= -0.32	p< 0.05	N = 48
Ca^{++} : Cyclosporine A, total daily dose, mg	R = -0.35	p< 0.05	N = 34
Pi : iPTH	R = -0.55	p< 0.00005	N = 48
Phosphate /24- hour urine : Cyclosporine A, total daily dose, mg	R = 0.43	p< 0.05	N = 34
TmP/GFR : iPTH	R = -0.479	p< 0.001	N = 48
TmP/GFR : Cyclosporine A, total daily dose, mg/kg BW	R = 0.41	p< 0.05	N = 34
Ca:Cr clearance ratio : Cyclosporine A, total daily dose, mg	R = -0.37	p< 0.05	N = 34
iPTH :ALP	R = 0.50	p< 0.0005	N = 48
iPTH : bALP	R = 0.47	p< 0.005	N = 45
iPTH : CrossLaps	R = 0.346	p< 0.05	N = 48
iPTH : 25(OH)D_3	R = -0.39	p< 0.01	N = 45
ALP : CrossLaps	R = 0.69	p< 0.0000	N = 48
bALP : CrossLaps	R = 0.70	p< 0.0000	N = 45
bALP : Cyclosporine A, trough level	R = 0.46	p< 0.01	N = 32

Table 4
Significant differences between patients on cyclosporine and patients on tacrolimus

Parameter	Patients on cyclosporine N= 34	Patients on tacrolimus N= 11	
Posttransplant period, months	22 (3-227)	11 (2-54)	P< 0.005
Pi, mmol/L	0.86 (061-1.19)	077 (0.46-0.90)	P< 0.05
TmP/GFR, mmol/L	0.56 (0.26-0.96)	0.51 (0.25-0.74)	P< 0.05

Conclusions

The majority of hypercalcemic kidney recipients had hyperparathyroidism. Furthermore, calcium urine excretion was in the majority of them as expected in hyperparathyroidism, but in 25% of them it was as in conditions caused by impaired sensitivity of calcium-sensing receptors. Thus, persisting hyperparathyroidism, but also the impairment of calcium-sensing receptor sensitivity, are pathogenetic factors for posttransplant hypercalcemia. Phosphate resorption was low and was related to iPTH. Cyclosporine nad tacrolimus might influence calcium and phosphate urine excretion. Further investigations are needed.

References

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Ruzica Smalcelj
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