Research Article

iMedPub Journals
www.imedpub.com

Journal of Emergency and Internal Medicine
ISSN 2576-3938

2019
Vol.3 No.1:2

Early Post Kidney Transplantation Hypophosphatemia

Maryam Ghorbani[1]* and Shahrzad Ossareh[2]

1 Department of Medicine, Ziaeean Hospital, Tehran University of Medical Sciences, Tehran, Iran
2 Department of Medicine, Nephrology Section, Hasheminejad Kidney Center, University of Medical Sciences, Tehran, Iran

***Corresponding author:**
Maryam Ghorbani

m.ghorbani82@yahoo.com

Department of Medicine, Ziaeean Hospital, Tehran University of Medical Sciences, Abozar st. Qazvin st- Tehran, Iran.

Tel: 98-9111287550

Citation: Ghorbani M, Ossareh S (2019) Early Post Kidney Transplantation Hypophosphatemia. J Emerg Intern Med Vol.3 No.1:2

Abstract

Background: Hypophosphatemia is one of the common complications after kidney transplantation (Tx). This study aimed to investigate the prevalence of hypophosphatemia in early post kidney Tx period and the associated risk factors.

Methods: Fifty renal transplant recipients were studied for serum phosphate (Pi) level on the day before (-1) and on 10 and 30 days after kidney Tx. Levels of serum creatinine (Cr), Pi, 25-hydroxyvitamin D (25(OH)D), intact PTH (iPTH) and FGF-23 and the 24 hour urinary excretion of Pi and Cr, estimated Glomerular Filtration Rate (eGFR) and the ratio of transport maximum of Pi to eGFR (TMP/GFR) were measured on the same days.

Results: Hypophosphatemia (serum Pi < 2.5 mg/dl) was observed in 0%, 40% and 42% of the patients On days -1, +10 and +30, respectively. There was no significant difference between 25(OH)D and iPTH levels in patients with and without hypophosphatemia on days +10 and +30. Pre-Tx FGF-23 level was significantly higher in patients with hypophosphatemia on days +10 and +30, compared to those with normophosphatemia in the same days(p=0.01 and p=0.04, respectively). Regression coefficient of TMP/GFR and Cr were positive on days -1 (p=0.01), +10 (p=0.001) and +30 (p=0.001). Coefficient of pre-Tx FGF-23 on post- Tx serum Pi was negative on days +10 (p=0.03)and +30 (p=0.003) and coefficient of post-Tx FGF-23 on day +10 with serum Pi was negative(p=0.008).

Conclusion: The main determinants of post-Tx hypophosphatemia in multivariate linear analysis were pre- Tx FGF-23, post-Tx FGF-23 levels on days +10, post-Tx Cr, and TMP/GFR.

Keywords: Hypophosphatemia; Kidney transplantation (Tx); Multivariate linear analysis

Received: April 10, 2019, **Accepted:** April 23, 2019 **Published:** April 30, 2019

Abbreviations

AZA: Azathioprine; CSA: Cyclosporine; Cr: Creatinine; DM: Diabetes mellitus; eGFR: Estimated Glomerular Filtration Rate; FGF-23: Fibroblast Growth Factor- 23; GN: Glomerulonephritis; HTN: Hypertension; iPTH: Intact PTH; MMF: Mycophenolate Mofetil; Pi: Phosphate; P: Prednisolone; RRT: Renal replacement therapy; Tx: Transplant; TAC: Tacrolimus; TMP/GFR: The Ratio of Transport Maximum of Pi to Estimated Glomerular Filtration Rate; 25(OH) D: 25-Hydroxyvitamin D

Introduction

Hypophosphatemia is a frequent complication after kidney transplantation (Tx) [1]. Hyperparathyroidism has been considered as one of the causes of hypophosphatemia after kidney Tx. But hypophosphatemia exists even after parathyroid hormone (PTH) level is normalized [2]. This indicates that other factors such as Fibroblast Growth Factor 23 (FGF-23) may also play a contributing role in hypophosphatemia after kidney Tx. FGF-23 is secreted by osteocytes in bone and has multiple functions such as regulation of calcium- phosphate metabolism and has a key role in the bone- kidney axis [3]. FGF-23 affects renal proximal tubule through down regulation of sodium-phosphate co-transporter (Na/Pi-co transporter type IIa and IIc) [4]. Through this effect it increases excretion of phosphate and acts as a phosphaturic hormone. FGF-23 inhibits 1α-hydroxylase, and up-regulates catabolic 24-hydroxylase pathway and therefore decreases the level of 1, 25(OH) D level (1). In addition to the

effects of FGF-23 on vitamin D metabolism, FGF-23 also inhibits PTH synthesis [5]. Recently elevated serum level of FGF-23 was suggested to play a role in the inappropriately low level of calcitriol and elevated renal phosphorous wasting in the early post-Tx period [6]. However the role of FGF-23 and other factors in the early post-Tx hypophosphatemia remains largely unknown [7].

Hypophosphatemia is caused by impaired renal tubular reabsorption and/or impaired intestinal inorganic phosphate absorption [8]. Renal proximal tubular phosphate reabsorption is mediated by Na/Pi-cotransporters IIa and IIc across the brush border membrane (BBM) [9]. There are a number of factors that contribute to the post-Tx hypophosphatemia, such as increased level or activity of PTH, relative deficiency of 1,25(OH)2D3, drugs (glucocorticoids, cyclosporine), phosphatonins and stanniocalcin. Phosphatonins are novel proteins regulating calcium and phosphate balance that include fibroblast growth factor-23 (FGF-23), secreted frizzled protein- 4 (sFRP-4), fibroblast growth factor-7 (FGF-7) and matrix extracellular phosphoglycoprotein (MEPE) [10]. Active vitamin D increases phosphate level by stimulating the Na/Pi-co transporters of the BBM of the renal proximal tubule and the upper small intestine.

The aim of this study was to investigate the prevalence of hypophosphatemia in the early post-Tx period and evaluate the associated risk factors such as kidney allograft function and the levels of FGF-23, 25(OH) D and PTH.

Methods

Study design and population

We performed a cohort study on 50 adult patients undergoing kidney Tx in Hasheminejad Kidney Center (HKC) between 2013 and 2016. The participants included patients of at least 18 years of age, admitted for kidney Tx. Patients were excluded from the study in case of lack of consent or loss from follow- up. Patients were studied during the first 30 days post- Tx. In 5 patients Tx was preemptive and in the others the mean dialysis vintage was 16.7 ± 15.55 (18-72) months.

Characteristics of the study population

Demographics and basic characteristics of study population are presented in **Table 1**. In 50 studied patients 74% were men and the mean age was 44 ± 10.4 years. In most of renal transplant recipients the underlying cause of CKD was unknown (24%) followed by diabetic nephropathy (20%), chronic glomerulonephritis (18%) and hypertension (18%). Ninety- four percent of patients had their first Tx and 88% had living and 12% had cadaveric donors.

Treatment regimens of the study population are presented in **Table 2**. The majority of patients (76%) received prednisolone, cyclosporine, and Mycofenolate mophetil. Normal allograft function was observed in 80% (n=40). For those with abnormal allograft function kidney biopsy was performed. According to biopsy reports, the acute rejection rate was 14% and the rate of ATN was 6%. Therapy with anti-thymoglobulin (ATG) was administered in 84% of patients (in 35 for induction and in 7 for rejection). None of the patients had history of parathyroidectomy prior to Tx and did not receive vitamin D after Tx.

Table 1 Demographics and basic characteristics (N=50).

Gender	No (%)
Male	37 (74)
Female	13 (26)
Age (mean ± SD) (yrs)	44±10.4
BMI (kg/m2)	24.5±3.7
Etiology of kidney disease	**No (%)**
Unknown	12 (24)
DM	10 (20)
Chronic GN	9 (18)
HTN	9 (18)
Others	10 (20)
Transplant	**No (%)**
First	47 (94)
Second	3 (6)
Donor	**No (%)**
Cadaver	6 (12)
Live donor	44 (88)
Dialysis Vintage (Mean ± SD) (mo)	16.7 ± 15.55
Parathyroidectomy	**No (%)**
Yes	0 (0%)
No	50 (100%)
DM=Diabetes mellitus, HTN=Hypertension, GN=Glomerulonephritis	

Table 2 Treatment characteristics (N=50).

Immunosuppressive	N (%)
P+CSA+MMF	38(76)
P+TAC +MMF	11 (22)
P+CSA+AZA	1 (2)
ATG	**N (%)**
For induction	35 (70)
For rejection	7 (14)
No ATG	8 (16)
Rejection	**N (%)**
No	40 (80)
Yes	7 (14)
ATN	3 (6)
Previous RRT	**N (%)**
Pre-emptive	5 (10)
Dialysis (n)	45 (90)
P=Prednisolone, MMF=Mycophenolate Mofetil, AZA=Azathioprine, CSA=cyclosporine, TAC=Tacrolimus, RRT=Renal replacement therapy	

Procedures, assays and calculations

Demographic data were collected. Fasting serum samples and 24 hours urine samples were obtained on the day before (-1) and on days 10 (+10) and 30 (+30) after kidney Tx. We measured the serum levels of creatinine (Cr), Calcium (Ca), inorganic phosphorus (Pi), Magnesium (Mg), potassium (K), 25- hydroxy vitamin D [25(OH)D], intact PTH (iPTH), and FGF-23 and the 24 hour urinary excretion of Pi, Cr and the ratio of transport maximum of Pi to estimated glomerular filtration rate (eGFR) (TMP/GFR).

In this study 25(OH) D was measured by enzyme-linked

immunosorbent assay (ELISA) (2nd Generation Short Incubation, Frankfurt, Germany). Enzyme-linked immunosorbent assay was also used for the measurement of human FGF- 23 (Immutopics Inc., San Clemente, CA, USA).

Intact PTH was measured using the Ad via centaur CP system. The Advia centaur assay is a two- site sandwich immunoassay. The cut-off point of iPTH for hyperparathyroidism according to KDIGO guidelines was considered as PTH >300 pg /dL in eGFR < 15 ml/min, PTH >110 pg /dL in eGFR=15-29 and PTH >70 pg /dL in eGFR >30 [11]. Serum levels of Cr, Ca, Pi, Mg and K were measured by standard assays using an automated analyzer (Bionik, USA).

Estimated GFR was calculated using the modification of diet in renal disease (MDRD) equation and TMP/GFR was calculated using the following equation:

TMP/GFR (mg/dl)=Serum Pi-(urine Pi × [serum Cr/urine Cr]). The normal range of TMP/GFR is 2.6 - 4.4 mg/dl.

Kidney transplantation protocols

The immune suppression prescription was according to the HKC protocol. All patients received 500 mg of parenteral methylprednisolone in the first three days of kidney Tx. Afterwards 1 mg/kg prednisolone was started orally, which was eventually decreased to 20-30 mg within one month. Mycophenolate mofetil (2 grams/day) or Mycophenolic acid (1440 milligrams/day) was started and a calcineurin inhibitor (Tacrolimus or cyclosporine) were prescribed according to targeted blood levels. Azathioprine was replaced for MMF in one patient due to gastrointestinal intolerance.

Statistical Analysis

We performed one way ANOVA to compare the changes of measured variables between the days -1, +10 and +30 of kidney Tx. The mean levels of the variables were compared using Duncan test. The measured variables were compared between hyperphosphatemic and normophosphatemic patients using t-test. The correlation between variables was assessed using Pearson correlation coefficient and finally we applied multivariate linear regression analysis. All data analyses were done using SPSS for Windows, Version 16.0. Chicago, SPSS Inc.

Results

The prevalence of post- Tx hypophosphatemia was 40% and 42% on days +10 and +30. The prevalence of hyperparathyroidism, and vitamin D deficiency also increased after transplantation **(Table 3)**.

The laboratory parameters were compared before and after kidney Tx. The mean pre- Tx Pi was 5.8 ± 1.7 mg/dL, which decreased to 3 ± 1.53 mg/dL and 2.74 ± 0.87 mg/dL at days +10 and +30, respectively. Mean post- Tx levels of eGFR significantly increased to 55.2 ± 18.8 and 56.9 ± 12.9 ml/min/1.73 m^2 at days +10 and +30, respectively. A significant reduction of serum K, 25(OH) D, PTH, FGF-23, and TMP/GFR was observed following Tx **(Table 4)**. The levels were not significantly different between days +10 and +30 after Tx, for any of these variables. The mean serum Ca slightly decreased after Tx from 9.05 ± 0.8 mg/dl at baseline to 8.92 ± 0.63 mg/dL at day +10, but a significant increase was found at day +30 (9.3 ± 0.51). Serum Mg level significantly decreased at the day +10 compared with day -1 (1.7 ± 0.23, vs. 2.34 ± 0.31), whereas it significantly increased to 2.5 ± 0.31 mg/dL at day +30 compared to pre-Tx level (p=0.001). The 24 hour urine Pi significantly increased at day +10 compared with day -1 (991 ± 488 vs. 41.5 ± 84.1 mg/day, p=0.0001), and it significantly decreased to 848 ± 229 mg/day at day +30 compared with day 10 (p=0.0001).

Compared with normophosphatemic patients, those with hypophosphatemia had significantly higher levels of eGFR and pre- Tx FGF-23. FGF-23 levels on days +10 and +30 were not different between hypo- and normophosphatemic patients **(Table 5)**. A higher level of K in hypophosphatemia patients was found

Table 3 Prevalence of Hypophosphatemia, Hyperparathyroidism, and Vitamin D deficiency.

Variables	Day -1	Day +10	Day +30
Hypophosphatemia (%)	0	40	42
Hyperparathyroidism (%)	34	66	52
Vitamin D deficiency (%)	32	42	46

Table 4 Comparison of laboratory parameters before and after kidney transplantation.

Variables	Day-1 (mean ± SD)	Day+10 (mean ± SD)	Day+30 (mean ± SD)	F	P
Pi (mg/dL)	5.8 ± 1.7^a	3 ± 1.53^b	2.74 ± 0.87^b	74.7	0.001
Cr (mg/dL)	8.6 ± 2.56^a	1.6 ± 1.2^b	1.33 ± 0.28^b	318.74	0.0001
eGFR (ml/min/1.73m2)	7 ± 2.55^a	55.2 ± 18.8^b	56.9 ± 12.9^b	198.51	0.001
Ca (mg/dL)	9.05 ± 0.8^a	8.92 ± 0.63^a	9.3 ± 0.51^b	5.67	0.004
Mg (mg/dL)	2.34 ± 0.31^a	1.7 ± 0.23^b	2.5 ± 0.31^c	50.78	0.001
K (mg/dL)	5.7 ± 0.7^a	4.4 ± 0.49^b	4.53 ± 0.61^b	20.16	0.0001
25(OH)D (ng/dL)	46.25 ± 2.57^a	37.01±1.76^b	35.61 ± 1.7^b	3.84	0.024
PTH (pg/dL)	286 ± 198^a	115 ± 101^b	95.22 ± 65.9^b	30.72	0.001
FGF-23 (pg/dL)	707 ± 897.5^a	181 ± 339.9^b	32.98 ± 39.18^b	20.43	0.0001
Urine Pi (mg/24h)	41.5 ± 84.1^a	991 ± 488^b	848 ± 229^c	110.98	0.0001
TMP/GFR	4.72 ± 2.5^a	1.48 ± 1.03^b	1.7 ± 0.95^b	59.25	0.01
Hb (g/dL)	12. 2 ± 2.3^a	10.8 ± 2.21^b	12.61 ± 1.8^a	9.53	0.001

only at day +10. Hypophosphatemic patients had lower levels of Cr and TMP/GFR compared with normophosphatemic patients in both days +10 and +30. The levels of PTH and 25(OH) D were not different between normophosphatemic and hypophosphatemia patients.

Correlations and Multivariate Analysis

The levels of serum Pi showed a significant positive correlation with Cr (r=0.86, p=0.001) and PTH (r=0.458, p=0.0001) at day +10. At day +10 a significant negative correlation was also found between the levels of serum Pi and FGF- 23 (r=- 0.324, p=0.028), Ca (r=-0.542, p=0.001). The serum Pi level was only significantly correlated with Cr (r=0.306, p=0.01) at day +30. Also, TMP/GFR was highly associated with serum Pi at days +10 (r=0.728, p=0.0001) and +30 (r=0.909, p=0.0001).

The assessment of multivariate linear regression analysis showed that the model was significant and a greater amount of R^2 was found on days +10 and +30 **(Table 6)**. Among the various variables the regression coefficients between serum Pi and serum Cr and TMP/GFR were significant and positive on days -1, +10 and +30. Also on day +10 we found a significant negative regression coefficient between FGF-23 and serum Pi.

In multivariate regression analysis pre- Tx FGF-23 had a significant negative regression coefficient with post- Tx Pi on days +10 and +30 **(Table 7)**.

We next examined the relationship between Pi and either FGF-23 or PTH in patients with high or low levels of 25(OH) D (≥ 30 or < 30 ng/dL) to see if vitamin D status has any effect on this relationship. We found that Pi was significantly associated with FGF-23 (r=0.675, p=0.006) in pre- Tx patients with 25(OH) D < 30 ng/dL. After Tx a negative correlation was found between Pi and FGF-23 only for patients with 25(OH) D ≥ 30 ng/dL (r=- 0.416, p=0.01 and r=- 0.428, p=0.022 at days +10 and +30, respectively). There was only a significant positive correlation between Pi and PTH (r=0.516, p=0.01) in patients with 25(OH) D < 30 ng/dL at day +10 **(Table 8)**.

Discussion

Kidney Tx correlates or improves many complications of chronic kidney disease(CKD) and is the best replacement option for end

Table 5 Changes of laboratory parameters before and after kidney transplantation in hypophosphatemic and normophosphatemic patients.

Variables	Day +10 (Mean ± SD)				Day +30 (Mean ± SD)			
	Hypo-Pi	Normo-Pi	T	p	Hypo-Pi	Normo-Pi	T	P
Pi (mg/dL)	1.83 ± 0.39	3.78 ± 1.51	6.78	0.001	1.91 ± 0.38	3.34 ± 0.6	10.37	0.001
Cr (mg/dL)	1.2 ± 0.22	1.88 ± 1.48	2.4	0.02	1.19 ± 0.14	1.43 ± 0.32	3.5	0.001
eGFR (ml/min/1.73m2)	64.67 ± 14.08	49.16 ± 19.2	3.29	0.002	62.8 ± 8.1	52.7 ± 14.2	3.19	0.003
Ca (mg/dL)	9.1 ± 0.5	8.8 ± 0.7	1.79	0.08	9.23 ± 0.48	9.44 ± 0.52	1.45	0.154
Mg (mg/dL)	1.77 ± 0.25	1.76 ± 0.24	0.06	0.95	1.85 ± 0.27	1.93 ± 0.37	0.87	0.38
K (mg/dL)	4.6 ± 0. 5	4.3 ± 0.45	2.17	0.036	4.52 ± 0.54	4.54 ± 0.67	0.13	0.89
25(OH)D(ng/d)	40.46 ± 18.3	34.63 ± 17.14	1.12	0.268	36.4 ± 22.3	35.1 ± 12.6	0.24	0.81
iPTH (pg/dL)	106.7 ± 76.66	120.8 ± 115.4	0.52	0.604	108.3 ± 65.44	85.75 ± 5.72	1.2	0.24
FGF-23 (pg/dL)	242.6 ± 381.03	139.9 ± 309.05	1.01	0.323	41.35 ± 48.9	26.92 ± 29.79	1.2	0.21
FGF-23 Pre-Tx (pg/dl)	1128.1 ± 1117.4	426.93 ± 582.7	2.58	0.03	1027.4 ± 1069.2	475.64 ± 678.7	2.08	0.04
Urine Pi (mg/24h)	1027.2 ± 500.85	967.8 ± 487.8	0.41	0.68	890.57 ± 291.76	817.52 ± 356.18	0.79	0.43
TMP/GFR	0.64 ± 0.44	2.05 ± 0.93	7.2	0.001	0.91 ± 0.38	2.29 ± 0.81	7.99	0.001
Hgb (mg/dL)	11.04 ± 2.63	10.71 ± 1.93	0.48	0.63	12.6 ± 1.87	12.61 ± 1.78	0.02	0.98

Table 6 Factors associated with serum Pi using multivariate linear regression model.

	Variables	Regression coefficient	P-value	R^2
Day -1	Cr (mg/dL)	0.301	0.01	65.9
	25(OH)D	-0.01	0.2	
	PTH (pg/dL)	-0.001	0.87	
	FGF-23 (pg/dL)	0.0003	0.203	
	TMP/GFR	0.26	0.003	
Day +10	Cr (mg/dL)	0.64	0.001	95.9
	25(OH)D	-0.006	0.077	
	PTH (pg/dL)	-0.0003	0.623	
	FGF-23 (pg/dL)	-0.0004	0.008	
	TMP/GFR	0.77	0.0001	
Day +30	Cr (mg/dL)	0.475	0.001	97.2
	25(OH)D	-0.002	0.27	
	PTH (pg/dL)	-0.0003	0.5	
	FGF-23 (pg / dL)	0.001	0.1	
	TMP/GFR	0.85	0.0001	

Table 7 Pre-transplant factors associated with serum Pi 10 and 30 days after transplant using.

Variables	Pre- Tx variables	Regression coefficient	P-value	R^2
Day +10	Cr (mg/ dL)	0.0009	0.99	14.3
	Vitamin D	0.001	0.87	
	PTH (Pg/ dL)	0.0002	0.84	
	FGF-23 (Pg/ dL)	-0.0006	0.03	
	TMP/GFR	-0.05	0.66	
Day +30	Cr (mg/ dL)	-0.1	0.09	36.7
	Vitamin D	0.003	0.39	
	PTH (Pg/ dL)	0.0004	0.56	
	FGF-23 (Pg/ dL)	-0.0004	0.003	
	TMP/GFR	0.01	0.833	

Table 8 Correlation between Serum Pi level, FGF23, PTH and 25(OH)D levels at different post Tx.

Variables	Serum Pi at Day -1		Serum Pi at Day +10		Serum Pi at Day +30	
	Low 25(OH)D*	Normal 25(OH)D**	Low 25(OH)D*	Normal 25(OH)D**	Low 25(OH)D*	Normal 25(OH)D**
Serum FGF23 R (P)	0.675 (0.006)	0.078 (0.66)	-0.068 (0.77)	-0.416 (0.01)	-0.130 (0.56)	-0.428 (0.02)
Serum PTH R (P)	0.037 (0.89)	0.209 (0.24)	0.516 (0.02)	0.247 (0.29)	-0.297 (0.18)	-0.197 (0.32)
*25(OH)D < 30 ng/dL, **25(OH)D ≥ 30 ng/dL						

stage kidney disease, but existing data suggest that kidney Tx only partially corrects mineral metabolism disorders, and persistent hyperparathyroidism may not be completely corrected [12,13].

In various studies hypophosphatemia has been a common complication after kidney Tx, with a frequency of 40% to 90% in the first month after successful Tx [14,15]. In our study hypophosphatemia was detected in 40% and 42% of the patients on days 10 and 30 after Tx, respectively. All cases had moderate hypophosphatemia (serum Pi=1 - 2.5 mg/dl) and no case of severe hypophosphatemia (serum Pi <1 mg/dl) was detected.

A number of studies have found that corticosteroids, calcineurin inhibitors (tacrolimus, cyclosporine) and mTOR inhibitors stimulate FGF-23 production. However, despite continuing relatively high doses of these drugs, resolution of hyperphosphatemia leads to reduction of FGF-23 in the first month after Tx. Glucocorticoids decrease tubular reabsorption of Pi by inhibition of Na/Pi-cotransporters of the renal proximal tubule and the upper small intestine. High doses of glucocorticoids and tacrolimus are correlated with phosphaturia, but are not believed to be the primary pathogenic factor of post- Tx hypophosphatemia. In our study almost all patients received the same immunosuppressive medications but about 40% of them developed hypophosphatemia and the level of hypophosphatemia was different between the patients.

Mean serum Pi level at days +10 and +30 was higher and the mean eGFR at those days was lower in cadaveric compared to living donor Tx. In cadaveric Tx the risk of delayed graft function and oliguria increases and this may lead to higher serum Pi levels and lower incidence of hypophosphatemia. Serum Pi level has an inverse correlation with kidney function and we showed that hypophosphatemic patients had lower serum Cr and higher eGFR.

The main regulators of phosphate in the kidney are FGF-23 and PTH [16,17]. The TMP/GFR ratio indicates renal loss of Pi. After Tx, despite normal allograft function, patients often have increased urinary excretion of Pi, decreased ratio of TMP/GFR and increased rate of fractional excretion of Pi. At the present study TMP/GFR was lower in hypophosphatemic patients than normophosphatemic patients at days +10 and +30. Also a strong positive correlation was observed between serum Pi and TMP/GFR at days +10 and +30. This finding was confirmed in the Multivariate linear regression analysis. In another study on 18 renal transplant patients, TMP/GFR was lower in hypophosphatemic patients, and a significant correlation was showed between TMP/GFR and Pi at 3, 6 and 12 months after Tx. This finding emphasizes on the role of increased phosphate excretion, and the role of phosphaturic hormones on post- Tx hypophosphatemia.

Vitamin D deficiency is common in general population, CKD patients and kidney Tx recipients. In this short-term follow- up study, the prevalence of 25 (OH)D deficiency (25(OH)D < 30 ng/ml) was 32%, 42% and 46% on days -1, +10 and +30, respectively. None of the patients had received vitamin D supplement after Tx. Vitamin D deficiency may be due to various factors including nutritional deficiency, malabsorption, low sun exposure, impaired kidney function, immunosuppressive drugs especially high dose of steroids, obesity and inflammatory state and a number of these factors are present after Tx and may explain increased incidence of vitamin D deficiency observed in our patients. PTH stimulates kidney 1 alpha hydroxylase, while FGF-23 suppresses 1 alpha hydroxylase [18]. Vitamin D level can increase serum Ca and Pi levels [19].

In our study mean 25(OH)D concentration significantly decreased on day +30 after Tx but the mean level was not significantly different between hypo- and normophosphatemic patients. We examined the relationship between serum Pi and 25(OH)D at days +10 and +30 but could not show any correlation between these. So it seems that 25(OH)D levels do not significantly influence the Pi level after Tx. We also examined the relationship between Pi with FGF-23 according to the levels of 25(OH)D (≥ 30 or < 30 ng/

dL) and found a negative correlation between serum Pi and FGF-23 only in patients with normal 25(OH)D on days +10 and +30. So it seems that after kidney Tx, the phosphaturic effect of FGF-23 can be exerted in the presence normal levels of vitamin D. This finding has not been previously observed and needs further evaluation.

Elevated PTH levels before Tx have been shown to decline during the first 3 months after kidney Tx. High PTH levels can be observed in 30-60% of kidney Tx recipients with good allograft function in the first year after kidney Tx. In the current study, PTH level significantly decreased after Tx but it was still higher than normal. According to normal values of PTH defined by KDIGO at different stages of CKD, the prevalence of hyperparathyroidism was 34%, 66% and 52%, on days -1, +10 and +30, respectively. Expectedly PTH production cannot reduce instantly after kidney Tx and the increase in eGFR and accordingly the sudden change in the definition of hyperparathyroidism, may complicate the interpretation. Actually it is not known at what post- Tx interval we should utilize the normal values of PTH for these patients, as in the general population. Any way in this study PTH level was not significantly different between normo-and hypophosphatemic patients, as a number of other studies have previously shown [20].

Patients with CKD and those on chronic dialysis often have high FGF-23 levels due to hyperphosphatemia, which significantly decreases and returns to baseline approximately at one year. According to investigations normal FGF-23 levels is less than 50 mg/dl. Our study showed that 88%, 52% and 16% of patients had high FGF-23 levels on days -1, +10 and +30. Despite the rapid reversal of high FGF-23 level during the early post- Tx period, and low prevalence of high FGF-23 on day +30, 42% of patients were still hypophosphatemic on day +30. Interestingly hypophosphatemic patients had significantly higher levels of pre- Tx FGF-23 compared with normophosphatemic patients, confirmed in multivariate analysis. In another study also the degree of post- Tx hypophosphatemia was predicted by pre-Tx FGF-23 level. This finding may show that residual FGF-23 function, maybe on receptor level, may play a role in post- Tx hypophosphatemia, despite rapid clearance of FGF-23 after Tx with normal functioning kidney.

Conclusion

Beyond the direct strong correlation between serum Cr, eGFR and TMP-GFR with low phosphate levels after kidney Tx, pre- Tx FGF-23 level is the best predictor of hypophosphatemia at early post- Tx period. Post- Tx FGF-23 on day +10 had also a negative correlation with serum Pi level. Optimal serum Pi control before kidney Tx, may help to prevent excessive rise of FGF 23 during and post- Tx hypophosphatemia. Contrary to our expectation, post-Tx hyperparathyroidism and hypovitaminosis D did not significantly influence post-Tx hypophosphatemia and this may be due to the strong effect of phosphatonins on serum Pi level. Further studies on other phosphaturic hormones, study of the effect of dietary phosphate intake and longer periods of follow up are suggested to find other possible risk factors.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1 Amiri FS, Khatami MR (2016) Fibroblast growth factor 23 in postrenal transplant: An often forgotten hormone. Exp Clin Transplant 14: 606–616.

2 Bhan I, Shah A, Holmes J, Isakova T, Gutierrez O, et al. (2006) Post-transplant hypophosphatemia: Tertiary “Hyper-Phosphatoninism”?. Kidney Int 70: 1486–1494.

3 Liu S, Quarles LD (2007) How fibroblast growth factor 23 works. Am Soc Nephrol 18: 1637–1647.

4 Taal MW, Chertow GM, Marsden PA, Skorecki K, Yu ASL, et al. (2011) Brenner and Rector’s The Kidney E-Book.

5 Sánchez-Fructuoso AI, Maestro ML, Calvo N, De La Orden V, Pérez-Flores I, et al. (2012) Role of fibroblast growth factor 23 (FGF23) in the metabolism of phosphorus and calcium immediately after kidney transplantation. Transplant Proc 44: 2551–2554.

6 Prasad N, Jaiswal A, Kumar S, Gupta A, Sharma RK, et al. (2016) FGF23 is associated with early post-Transplant hypophosphataemia and normalizes faster than iPTH in living donor renal transplant recipients: A longitudinal follow-up study. J Clin Kidney 9: 669–676.

7 Economidou D, Dovas S, Papagianni A, Pateinakis P, Memmos D (2009) FGF-23 Levels before and after Renal Transplantation. J Transplant 1: 1–5.

8 Seifi S, Pezeshki ML, Khatami MR, Mazdeh MM, Ahmadi F, et al. (2003) Post-renal transplantation hypophosphatemia. Transplant Proc 35(7): 2645–2646.

9 Sakhaee K (2010) Post-renal transplantation hypophosphatemia. Pediatr Nephrol 25: 213–220.

10 Shaikh A, Berndt T, Kumar R (2008) Regulation of phosphate homeostasis by the phosphatonins and other novel mediators. J Int Pediatr Nephrol Assoc 23: 1203–1210.

11 Uribarri J (2003) K/DOQI Clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 46:4.

12 Wolf M, Weir MR, Kopyt N, Mannon RB, Von-Visger J, et al. (2009) A Prospective Cohort Study of Mineral Metabolism After Kidney Transplantation. Transplant 100(1): 184-193.

13 Pahnwat T, Taweesedt P, Disthabanchong S (2015) Mineral and bone disorder after kidney transplantation. World J Transplant 5(4): 231–242.

14 Evenepoel P, Meijers BKI, De Jong H, Naesens M, Bammens B, et al. (2008) Recovery of hyperphosphatoninism and renal phosphorus wasting one year after successful renal transplantation. Clin J Am Soc Nephrol 3: 1829–1836.

15 Huber L, Naik M, Budde K (2013) Frequency and long-term outcomes of post-transplant hypophosphatemia after kidney transplantation. Transpl Int 26: 94–96.

16 Morrin M, O’Keane M, Kilbane M, Mc Kenna M (2014) The effect of FGF23 on renal phosphorus handling is dependent on PTH secretion. EJEA Endocr Abstr.

17 Stavroulopoulos A, Cassidy MJD, Porter CJ, Hosking DJ, Roe SD (2007) Vitamin D Status in Renal Transplant Recipients Vitamin D status is low in virtually all the renal transplant recipients in a study in central England. Am J Transplant 7: 2546–2552.

18 Gutierrez O (2005) Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. J Am Soc Nephrol 16: 2205–2215.

19 Liu WC, Wu CC, Hung YM, Liao MT, Shyu JF, et al. (2016) Pleiotropic effects of vitamin D in chronic kidney disease. CCA Clin Chim Acta 453: 1–12.

20 Han SY, Hwang EA, Park SB, Kim HC, Kim HT (2012) Elevated fibroblast growth factor 23 levels as a cause of early post-renal transplantation hypophosphatemia. TPS Transplant Proc 44: 657–660.