

Early postkidney transplantation hypophosphatemia

Maryam Ghorbani¹, Shahrzad Ossareh²

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

Background: As hypophosphatemia is a common multifactorial problem of kidney transplantation (Tx), this research aimed at studying the frequency of posttransparent hypophosphatemia in the early postkidney Tx period and investigating the risk components associated with the situation. **Materials and Methods:** In this study, 50 renal transplant recipients on the day before (-1) and on days 10 (+10) and 30 (+30) days after kidney Tx were examined for the levels of serum phosphate (Pi). Levels of serum creatinine (Cr), Pi, 25-hydroxyvitamin D (25[OH] D), intact parathyroid hormone (iPTH) and fibroblast growth factor 23 (FGF-23), the 24 h urinary excretion of Pi and Cr, estimated glomerular filtration rate (eGFR), and the ratio of transport maximum of Pi (TMP) to eGFR (TMP/GFR) were evaluated on the same days. **Results:** Hypophosphatemia (serum Pi <2.5 mg/dl) was seen in 0%, 40%, and 42% of the patients on days -1, +10, and +30, respectively. The levels of 25(OH)D and iPTH were not significantly different in patients with and without hypophosphatemia on days +10 and +30. Compared to those with normophosphatemia, pre-Tx FGF-23 level was significantly higher in patients with hypophosphatemia on days +10 and +30, respectively. The regression coefficient of TMP/GFR and Cr was positive on days -1, +10, and +30. The 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 the coefficient of post-Tx FGF-23 was negative just on day +10 with serum Pi ($P < 0.008$). **Conclusion:** The main causes of post-Tx hypophosphatemia in the multivariate linear analysis were pre-Tx FGF-23 and post-Tx FGF-23 levels on days +10, post-Tx Cr, and TMP/GFR.

Key words: Hypophosphatemia, kidney, multivariate analysis, transplantation

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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. However, hypophosphatemia exists even after the parathyroid hormone (PTH) level is normalized.^[2,3] 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.^[4] FGF-23 affects renal proximal tubule through the downregulation of sodium-phosphate co-transporter (Na/Pi-co transporter

Type IIa and IIc).^[5] Through this effect, it increases the excretion of phosphate and acts as a phosphaturic hormone.^[6] FGF-23 inhibits 1 α -hydroxylase and upregulates catabolic 24-hydroxylase pathway, and therefore, decreases the level of 1, 25-hydroxyvitamin D (25[OH] D) level.^[1] In addition to the effects on Vitamin D metabolism, FGF-23 also inhibits PTH synthesis.^[6] Recently, elevated serum level of FGF-23 was suggested to play a role in the inappropriately low level of calcitriol and elevated renal phosphorus wasting in the early post-Tx period.^[7] However, the role of FGF-23 and other factors in the early post-Tx hypophosphatemia remain largely unknown.^[8]

There are a number of factors that contribute to the post-Tx hypophosphatemia, such as increased level

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Address for correspondence: Dr. Maryam Ghorbani, Department of Medicine, Ziaeean Hospital, Tehran University of Medical Sciences, Abozar Street, Qazvin Street, Tehran, Iran. E-mail: mghorbanip@sina.tums.ac.ir

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of activity of PTH, relative deficiency of $1,25(\text{OH})_2\text{D}_3$, drugs (glucocorticoids and cyclosporine), phosphatonins, and stanniocalcin.^[9,10] Calcium and phosphate balance is regulated by phosphatonins which include FGF-23, secreted frizzled protein-4 (sFRP-4), FGF-7, and matrix extracellular phosphoglycoprotein.^[11] 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, $25(\text{OH})\text{D}$ and PTH.

MATERIALS AND METHODS

Study design and population

We performed a cohort study on 50 adult patients undergoing kidney Tx in Hasheminejad Kidney Center of Tehran between 2013 and 2016. This study was approved by the Iran University of Medical Sciences (Research Project number: 90-01-30-12259). 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 the follow-up. Patients were studied during the first 30 days post-Tx. All patients present until the last follow-up.

Characteristics of the study population

Demographics and basic characteristics of the study population are presented in Table 1, and treatment regimens of the study population are provided in Table 2. In pretransplant, none of the patients had a history of parathyroidectomy and cinacalcet use. The history of other drugs in pretransplant was not taken. After transplantation, none of the patients received cinacalcet, rocalcrol, and other components of Vitamin D, renagel, and diuretic.

Procedures, assays, and calculations

Demographic data were collected. Fasting serum samples and 24-h 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), $25(\text{OH})\text{D}$, intact PTH (iPTH), and FGF-23 and the 24 h urinary excretion of Pi, Cr, and the ratio of transport maximum of Pi to estimated glomerular filtration rate (eGFR) (TMP/GFR).

In this study, $25(\text{OH})\text{D}$ was measured by enzyme-linked immunosorbent assay (ELISA) (2nd-Generation Short Incubation, Frankfurt, Germany). ELISA was also used for the measurement of human FGF-23 (Immutopics Inc., San Clemente, CA, USA).

Intact PTH was measured using the Advia Centaur CP system. The Advia Centaur assay is a two-site

Table 1: Demographics and basic characteristics (n=50)

Variables, No (%)	Respectively
Gender, n (%)	
Male	37 (74)
Female	13 (26)
Age (mean±SD) (years)	44±10.4
BMI (kg/m ²), n (%)	24.5±3.7
Etiology of kidney disease, n (%)	
Unknown	12 (24)
DM	10 (20)
Chronic GN	9 (18)
HTN	9 (18)
Others	10 (20)
Transplant, n (%)	
First	47 (94)
Second	3 (6)
Donor, n (%)	
Cadaver	6 (12)
Live donor	44 (88)
Hemodialysis vintage (mean±SD) (months)	16.7±15.55
Parathyroidectomy, n (%)	
Yes	0
No	50 (100)

DM=Diabetes mellitus; HTN=Hypertension; GN=Glomerulonephritis; SD=Standard deviation; BMI=Body mass index

Table 2: Treatment characteristics (n=50)

	n (%)
Immunosuppressive	
P+CSA+MMF	38 (76)
P+TAC+MMF	11 (22)
P+CSA+AZA	1 (2)
ATG	
For induction	35 (70)
For rejection	7 (14)
No ATG	8 (16)
Rejection	
No	40 (80)
Yes	7 (14)
ATN	3 (6)
Previous RRT	
Preemptive	5 (10)
Dialysis (n)	45 (90)

P=Prednisolone; MMF=Mycophenolate Mofetil; AZA=Azathioprine; CSA=Cyclosporine; TAC=Tacrolimus; RRT=Renal replacement therapy; ATG=Anti thymocyte globulin; ATN=Anti tubular necrosis

sandwich immunoassay. The cutoff point of iPTH for hyperparathyroidism according to the KDIGO guidelines was considered as PTH > 300 pg/dL in eGFR <15 cc/min/1.73 m², PTH >110 pg/dL in eGFR = 15–29 cc/min/1.73 m², and PTH >70 pg/dL in eGFR > 30 cc/min/1.73 m².^[12] 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 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.^[5]

Statistical analysis

The prevalence of post-Tx hypophosphatemia was 40% and 42% on days +10 and +30 [Table 3], respectively. The prevalence of hyperparathyroidism and Vitamin D deficiency also increased after transplantation [Table 3].

The laboratory parameters were compared before and after kidney Tx by the repeated analysis of variance [Table 4].

Table 3: Prevalence of hypophosphatemia, hyperparathyroidism, and Vitamin D deficiency

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

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 [Table 4]. Mean post-Tx levels of eGFR significantly increased to 55.2 ± 18.8 and 56.9 ± 12.9 ml/min/1.73 m² at days +10 and +30, respectively [Table 4]. A significant reduction of serum K, 25(OH)D, PTH, FGF-23, and TMP/GFR was observed following Tx.

Compared with normophosphatemic patients, those with hypophosphatemia had significantly higher levels of eGFR and pre-Tx FGF-23 [Table 5]. The assessment of multivariate linear regression analysis showed that the model was significant and a greater amount of R² was found on days +10 and +30 [Table 6].

In multivariate regression analysis, pre-Tx FGF-23 had a significant negative regression coefficient with post-Tx

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

Variable	Mean±SD			F	P<
	Day -1	Day +10	Day +30		
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/1.73 m ²)	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/24 h)	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

SD=Standard deviation; Pi=Inorganic phosphorus; Cr=creatinine; Ca=Calcium; eGFR=Estimated glomerular filtration rate; Mg=Magnesium; K=Potassium; 25(OH) D=25-hydroxy vitamin D; PTH=Parathyroid hormone; FGF-23=Fibroblast growth factor 23; TMP/GFR=The ratio of transport maximum of Pi to estimated Glomerular Filtration Rate; Hb=Hemoglobin; ^{a,b,c}: Not applicable

Table 5: Changes of laboratory parameters before and after kidney transplantation

Variables	Day+10				Day+30			
	Mean±SD		T	P<	Mean±SD		T	P<
	Hypo-Pi	Normo-Pi			Hypo-Pi	Normo-Pi		
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/1.73 m ²)	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	426.93±582.7	2.58	0.03	1027.4±1069.2	475.64±678.7	2.08	0.04
Urine Pi (mg/24 h)	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
Hb (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

Tx=Transplantation; SD=Standard deviation; Pi=Inorganic phosphorus; Ca=Calcium; eGFR=Estimated glomerular filtration rate; Mg=Magnesium; K=Potassium; 25(OH) D=25-hydroxy vitamin D; PTH=Parathyroid hormone; FGF-23=Fibroblast growth factor 23; TMP/GFR=The ratio of transport maximum of Pi to estimated Glomerular Filtration Rate; Hb=Hemoglobin; iPTH=Intact PTH

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-stage kidney disease. Existing data suggest that kidney Tx only partially corrects mineral metabolism disorders and persistent hyperparathyroidism may not be completely corrected.^[13,14]

Hypophosphatemia is a common complication after kidney Tx, with a frequency of 40%–90% in the 1st month after successful Tx.^[15,16] 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.

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.^[2]

Serum Pi level has an inverse correlation with kidney function,^[2] and we showed that hypophosphatemic patients had lower serum Cr and higher eGFR.

The main regulators of phosphate in the kidney include FGF-23 and PTH.^[17] The TMP/GFR ratio indicates renal loss of Pi.^[17] 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.^[9] In the present study, TMP/GFR was lower in hypophosphatemic patients than normophosphatemic patients at days +10 and +30. Furthermore, 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 shown between TMP/GFR and Pi at 3, 6, and 12 months after Tx.^[8] This finding emphasizes the role of increased phosphate

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

Day	Variables	Regression coefficient	P	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	

$P < 0.05$ is considered as statistically significant. Cr=Creatinine; 25(OH)D=25-hydroxy vitamin D; PTH=Parathyroid hormone; FGF-23=Fibroblast growth factor 23; Pi=Inorganic phosphorus; TMP/GFR=The ratio of transport maximum of Pi to estimated glomerular filtration rate

Table 7: Pretransplant factors associated with serum inorganic phosphorus 10 and 30 days

Day	Pre-Tx variables	Regression coefficient	P	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	

Cr=Creatinine; PTH=Parathyroid hormone; FGF-23=Fibroblast growth factor 23; Pi=Inorganic phosphorus; TMP/GFR=The ratio of transport maximum of Pi to estimated glomerular filtration rate; Tx=Transplantation

Table 8: Correlation between serum inorganic phosphorus level, fibroblast growth factor 23, parathyroid hormone, and 25-hydroxy vitamin D levels

Variable	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 FGF-23, 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. PTH=Parathyroid hormone; FGF-23=Fibroblast growth factor 23; 25(OH)D=25-hydroxy vitamin D; Pi=Inorganic phosphorus

excretion and the role of phosphaturic hormones on post-Tx hypophosphatemia. Mean Pi level of urine in 24 h for 1, +10, and +30 days was 41.5, 991, and 848 mg/dl, respectively. According to the analysis of variance, there was a significant difference between -1 and +10 and between -1 and +30.

Vitamin D deficiency is common in the general population, CKD patients, and kidney Tx recipients.^[2] 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 supplements 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 the increased incidence of Vitamin D deficiency observed in our patients.^[14,18]

In our study, mean 25(OH)D concentration significantly decreased on day +30 after Tx, but the mean level was not significantly different between hypophosphatemic 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. Hence, 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. Hence, 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.^[14] High PTH levels can be observed in 30%–60% of kidney Tx recipients with good allograft function in the 1st year after kidney Tx.^[14] In the current study, PTH level significantly decreased after Tx, but it was still higher than normal. According to the 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. In fact, 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. Anyway in this study, PTH level was not significantly different between normo- and hypophosphatemic patients, as a number of other studies have previously shown.^[7,19]

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 1 year.^[14] According to the investigations, normal FGF-23 levels are <50 mg/dl.^[8] 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.^[8] This finding may show that residual FGF-23 function,^[19] maybe on receptor level, may play a role in post-Tx hypophosphatemia, despite rapid clearance of FGF-23 after Tx with normal functioning kidney.

Limitations and suggestions

This study had some limitations such as small sample size and the short period of follow-up. Further studies on other phosphaturic hormones, besides fixing these limitations can study the effect of dietary phosphate intake and longer periods of follow-up are suggested to find other possible risk factors.

CONCLUSION

Beyond the direct strong correlation between serum Cr, eGFR, and TMP-GFR with low phosphate levels after kidney Tx, the 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 the 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.

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Conflicts of interest

There are no conflicts of interest.

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