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The incidence of hypophosphatemia in the early posttransplant period in renal transplant recipients and its association with graft function

Emel Işıktaş Sayılar

Department of Nephrology, Ufuk University School of Medicine, Dr. Rıdvan Ege Hospital, Ankara, Turkey

ABSTRACT

Objectives: To investigate the prevalence of posttransplant hypophosphatemia in the early posttransplant period among renal transplant recipients in relation to its impact on renal graft function.

Methods: A total of 78 renal transplant recipients who were transplanted between January 2016 and March 2020 were included in this retrospective single center study. Data on laboratory findings (phosphate, creatinine, estimated glomerular filtration rate [eGFR], albumin, serum corrected calcium and parathyroid hormone [PTH] levels) at pre- and posttransplant 3 month follow up period were recorded.

Results: Hypophosphatemia was detected in 16 (20.8%), 13 (16.7%) and 7 (9.1%) patients at the posttransplant day 10, month 1 and month 3, respectively. Posttransplant day 10 and day 30 measurements revealed significantly lower serum creatinine values ($p < 0.001$ and $p < 0.07$, respectively) and significantly higher eGFR values ($p = 0.009$ and $p = 0.036$, respectively) in the hypophosphatemic group compared to the normophosphatemic group. Serum phosphate displayed linear relationship with creatinine at day 10 ($r = 0.687$, $p < 0.001$), day 30 ($r = 0.301$, $p = 0.007$), while not correlated with PTH levels at posttransplant day 10, day 30 and day 90.

Conclusions: Our findings suggest that hypophosphatemia is common in the early posttransplant period, particularly first month after kidney transplantation, being associated with better renal graft function.

Keywords: Hypophosphatemia, kidney transplantation, graft function

Hypophosphatemia is a prevalent complication observed in 40-90% of renal transplant patients in the posttransplant first month [1]. In chronic kidney disease (CKD), along with a decline in eGFR, phosphaturic hormones such as parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF-23) increase in response to phosphate retention and inhibit renal tubular phosphate reabsorption [2, 3]. As kidney function recovers after kidney transplantation, the accumulated FGF-23 and PTH exaggerate renal tubular phosphate leak, leading to phosphate depletion. With normalization of PTH and FGF-23 levels toward baseline, serum phosphate levels gradually increase and reach the normal limits within 12 months [4-6].

Although hypophosphatemia is considered likely to be associated with a good graft function and prolonged graft survival, the clinical relevance of posttransplant hypophosphatemia remains unclear in terms of graft survival exact [7].

This study aimed to evaluate the relationship be-

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Address for correspondence: *Emel Işıktaş Sayılar, MD., Assistant Professor, Ufuk University School of Medicine, Dr. Rıdvan Ege Hospital, Department of Nephrology, 06830 Balgat, Ankara, Turkey. E-mail: emelisiktas@yahoo.com, GSM: +90 507 9648090, Fax: +90 312 2044266*

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tween serum phosphate levels and graft function in renal transplant patients within the first 3 months of posttransplant period.

METHODS

Study Population

Seventy eight consecutive adult patients who underwent renal transplantation between January 2016 and March 2020 were included in this retrospective single center study. Inclusion criteria were receiving ABO-compatible first-time kidney transplantation at least 1 year ago, while exclusion criteria were being under the age of 18 and history of pretransplant parathyroidectomy. There was no current or previous noncalcium-containing phosphate binder, vitamin D analog, or calcimimetic use in any of the patients. Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the Ufuk University Faculty of Medicine Ethics Committee (Protocol no: 20200703/2).

Assessments

Data on patient demographics, clinical and laboratory findings, tacrolimus levels and follow-up records were collected from the hospital database. Patients were followed up during the first 90 days of posttransplant period and data on routine laboratory tests (creatinine, phosphate, calcium, albumin, parathyroid hormone levels) were recorded before transplantation and on posttransplant 10th day, 1st month and 3rd months. Posttransplant hypophosphatemia was defined as serum phosphate level < 2.3 mg/dL. Serum calcium was corrected based on the following equation: Corrected Ca (mg/dL) = Serum Calcium + [(4.0 – albumin (g/dL)) × 0.8)] [8]. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease formula [9].

Treatments

When indicated anti-thymocyte globulin (ATG, Grafalon Neovii) was administered at 100 mg/g dose for 3 days. Following total 1500 mg intravenous methyl-prednisolone, all patients were administered prednisolone (0.8 mg/kg/day, orally). Prednisolone dose was tapered to 30 mg/day at 1 month, 20 mg/day at 2 months and 5 mg/day after 3 months. In the maintenance treatment phase, calcineurin inhibitor [tacrolimus (Tac); 0.1 mg/kg/day, 2 doses per day] and antiproliferative agent (mycophenolate mofetil; maximum 2 g/day or mycophenolate sodium; maximum 1440 mg/g) were used along with prednisolone. Tac doses were titrated as needed to achieve target blood levels. In case of acute rejection, renal biopsy was performed and treatment (pulse methyl-prednisolone, ATG, plasmapheresis, and intravenous immunoglobulin treatments alone or in combination) was administered according to Banff criteria [10].

Statistical Analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY). The Student-t test was used to compare the findings in hypophosphatemic and normophosphatemic groups for each time period. The Pearson correlation analysis was used to measure the strength of a linear association between serum phosphate and other variables and then Simple Linear Regression analysis was performed for further analysis. Data were expressed as mean± standard deviation (SD), median (interquartile range) and percent (%) where appropriate. $P < 0.05$ was considered statistically significant.

RESULTS

Of the patients, 21.8% were female and 78.2% were male. The mean age was 43 ± 14 years and median follow-up period was 28 (ranged, 15 to 40) months. The underlying causes of end-stage renal disease involved chronic glomerulonephritis in 32 (41%) patients, hypertension in 17 (20.8%) patients, type 2 diabetes mellitus in 12 (15.4%) patients and secondary amyloidosis in 10 (12.8%) patients, while nephrolithiasis, polycystic kidney disease and no detectable cause were noted in 2 (2.6%), 2 (2.6%) and 3 (3.8%) patients, respectively. During follow-up, acute allograft rejection occurred in 16 (20.5%) patients. Dialysis type, number of tissue adaptation, type of transplantation, type of induction and maintenance immunosuppression treatment features are shown in Table 1.

The mean pretransplant phosphate level was 4.2 ±

Table 1. Patient demographics and baseline characteristics

Variables	n = 78
Gender, F/M, n (%)	17/61 (21.8/78.2)
Age, (year, mean ± SD)	43 ± 14
Type of dialysis, n (%)	
Preemptive	40 (51.3)
Hemodialysis	37 (47.4)
Peritoneal dialysis	1 (1.3)
Transplant type (live/cadaver)	75/3 (96.2/3.8)
Miss-Match count, n (%)	
0 MM	3 (3.8)
1 MM	7 (9.0)
2 MM	10 (12.8)
3 MM	26 (33.3)
4 MM	14 (17.9)
5 MM	9 (11.5)
6 MM	9 (11.5)
Transplant duration (month, median, IQR)	28 (15-40)
Induction treatment, n (%)	
ATG	34 (43.6)
None	44 (56.4)
Maintenance treatment	
Tac+MMF	61 (78.2)
Tac+MFA	17 (20.8)
Acute rejection, n (%)	16 (20.5)

SD = standard deviation, F =female, M = male, MM = miss-match, Tac = tacrolimus, ATG = anti-thymocyte globulin, MFA = mycophenolic acid, MMF = mycophenolate mofetil, IQR = interqartile

1.37mg/dL, which decreased to 3.2 ± 1.01mg/dL, 3.2 ± 0.86 mg/dL, and 3.4 ± 0.70 mg/dL at the posttransplant day 10, month 1 and month 3, respectively. Hypophosphatemia was detected in 16 (20.8%), 13 (16.7%) and 7 (9.1%) patients at the posttransplant day 10, month 1 and month 3, respectively. Mean posttransplant levels of creatinine significantly decreased to 1.65 ± 1.10 mg/dL, 1.37 ± 0.60 mg/dL, and 1.39 ± 0.43mg/dL at the posttransplant day 10, month 1 and month 3, respectively. The mean pretransplant PTH level was 418.14 ± 400.75 ng/L and decreased to 184.55 ± 135.38 ng/L, 202.46 ± 132.66 ng/L, and 134.31 ± 95.62 ng/L at the posttransplant day 10, month 1 and month 3, respectively. When compared to pre-transplant laboratory parameters, significant difference was noted in post-transplant parameters for 10th day, 1st month and 3rd month ($p < 0.05$) (Table 2).

Posttransplant day 10 and day 30 measurements revealed significantly lower serum creatinine values ($p < 0.001$ and $p < 0.07$, respectively) and significantly higher eGFR values ($p = 0.009$ and $p = 0.036$, respectively) in the hypophosphatemic group compared to the normophosphatemic group (Table 3, Fig. 1 and Fig. 2).

Serum phosphate displayed linear relationship with creatinine at day 10 (r = 0.687, $p < 0.001$), day 30 (r = 0.301, $p = 0.007$) and day 90 (r = 0.070, $p = 0.548$) and inverse relationships with eGFR at day 10 (r = -0.461, $p < 0.001$), day 30 (r = -0.157, $p = 0.171$)

Table 2. Laboratory parameters before and after transplantation

	Pretransplant	Posttransplant		
Variables, mean ± SD	Day -1	Day +10	Day +30	Day +90
P (mg/dL)	4.2 ± 1.37	3.2 ± 1.01	3.2 ± 0.86	3.4 ± 0.70
Cr (mg/dL)	4.62 ± 1.62	1.65 ± 1.10	1.37 ± 0.60	1.39 ± 0.43
eGFR (ml/min/1.73m^2)	15.39 ± 5.69	60.26 ± 25.59	67.33 ± 22.24	67.24 ± 23.83
c-Ca (mg/dL)	9.89 ± 0.64	9.63 ± 0.89	9.73 ± 0.43	9.53 ± 0.89
PTH (ng/L)	418.14 ± 400.75	184.55 ± 135.38	202.46 ± 132.66	134.31 ± 95.62

Data are shown are mean±standard deviation. c-Ca = corrected calcium, Cr = creatinine; eGFR = estimated glomerular filtration rate, P = phosphate; PTH = parathyroid hormone

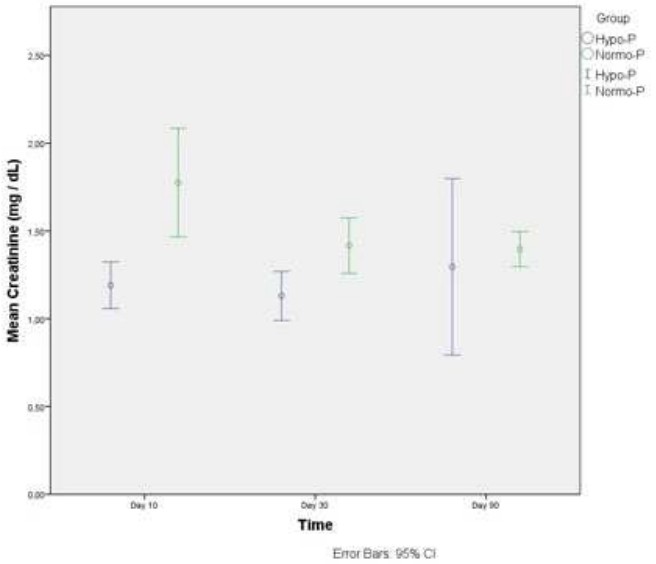

Fig. 1. Comparison of posttransplant creatinine values of hypophosphatemic and normophosphatemic groups.

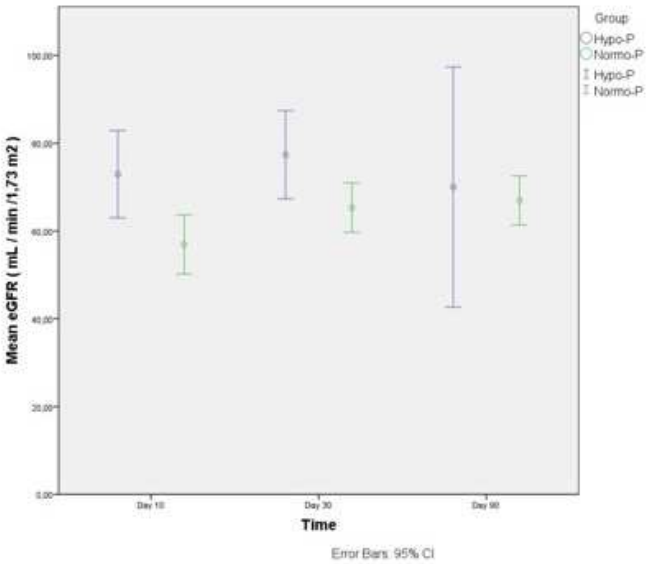

Fig. 2. Comparison of posttransplant eGFR values of hypophosphatemic and normophosphatemic groups.

and day 90 (r = -0.013, p = 0.911). No significant correlation was noted between serum phosphate and PTH levels at day 10 (r = -0.134, p = 0.416), day 30 (r = -0.262, p = 0.163) and day 90 (r = -0.184, p = 0.388).

DISCUSSION

In the early posttransplant stage, the relatively high FGF-23 and PTH concentrations in relation to restored renal excretory capacity of phosphate may result in hypophosphatemia, especially within the first year [11]. In a past study by Ghorbani *et al*. [5] in 50 kidney transplant patients, hypophosphatemia was reported in 42% of patients in the first posttransplant month. In the current study, hypophosphatemia was noted in 13 (16.7%) patients in the in the first posttransplant month.

Our findings related to association of the development of hypophosphatemia with a lower creatinine and higher eGFR values seems to be in accordance with consideration of good graft function to be accompanied by an increased renal capacity to excrete phosphate in early after transplantation. Identification of lower creatinine levels and higher eGFR values in our hypophosphatemic patients than in normophosphatemic patients at posttransplant day 30 indicates an inverse correlation between serum phosphate levels and kidney function. Likewise, in a past study by Seifi *et al*. [12] with 237 transplant patients, hypophosphatemia was reported in 58% of patients within the first 2 months of the posttransplant period, while au-

thors also noted significantly lower serum creatinine levels in hypophosphatemic vs. normophosphatemic patients [12]. In a past study among 90 renal transplant patients, presence of hypophosphatemia at the post-transplant first month and 3rd month but not at the posttransplant 12th month was reported to be an independent predictor of good kidney survival [3].

Elevated PTH levels before transplantation have been shown to decline during the first 3 months after kidney transplantation. High PTH levels can be observed in 30-60% of kidney transplant recipients with good allograft function in the 1st year after kidney transplantation. PTH production cannot reduce instantly after kidney transplantation, and along with the increase in eGFR, the sudden change in the definition of hyperparathyroidism may complicate the interpretation [13]. Similar to our findings, there studies in the literature indicated no significant difference between normo- and hypophosphatemic patients in terms of PTH levels [5, 14]. Bhan *et al*. [15] reported that pre-transplant PTH elevation was not a risk factor for post-transplant hypophosphatemia, while FGF-23 levels were independently associated with decreased serum phosphate levels. In the current study, since FGF-23 levels were not measured, the association between FGF-23 levels and posttransplant hypophosphatemia could not be analyzed.

The high-dose steroids and tacrolimus are considered to be associated with renal phosphate wasting. However, while hypophosphatemia is commonly noted after kidney transplantations, it does not typically develop after other solid organ transplants despite use of similar and often higher doses of immunosuppressive regimens [16, 17]. In the current study, while almost all patients were on an identical immunosuppressive regimen, only some patients developed hypophosphatemia. Accordingly, immunosuppressive agents, whilst may induce phosphaturia after renal transplantation, seem unlikely to be the primary cause of hypophosphatemia.

Limitations

The major limitations of the current study seem to be the small sample size and lack of data on FGF-23 levels, 25(OH)D vitamin levels and fractional phosphate excretion at pre- and post-transplant period as well as on the dietary phosphate intake.

Table 3. Association of hypophosphatemia with creatinine, eGFR and PTH levels at the posttransplant 10, 30 and 90 days

	Day 10			Day 30			Day 90		
Variables	**Hypo-P**	**Normo-P**	***p value***	**Hypo-P**	**Normo-P**	***p value***	**Hypo-P**	**Normo-P**	***p value***
P	1.98 ± 0.27	3.51 ± 0.88	**< 0.001**	2.02 ± 0.25	3.48 ± 0.71	**< 0.001**	2.03 ± 0.28	3.49 ± 0.58	**< 0.001**
Cr	1.19 ± 0.25	1.78 ± 1.21	**< 0.001**	1.13 ± 0.23	1.42 ± 0.64	**0.007**	1.30 ± 0.54	1.40 ± 0.42	0.556
eGFR	72.93 ± 18.66	56.94 ± 26.24	**0.009**	77.38 ± 16.62	65.33 ± 22.77	**0.036**	70.00 ± 29.59	66.96 ± 23.42	0.750
PTH	226.56 ± 180.65	175.37 ± 125.16	0.498	170.10 ± 128.47	210.55 ± 135.13	0.514	186.70 ± 100.16	132.03 ± 97.10	0.587

Data are shown are mean±standard deviation. Cr = creatinine; eGFR = estimated glomerular filtration rate; P = phosphate; PTH = parathyroid hormone; SD = standard deviation

CONCLUSION

In conclusion, hypophosphatemia is frequently seen after renal transplantation in relation to the functional performance of the transplanted kidney. Our data also suggest that the impact of hypophosphatemia on graft survival is influenced by the time after kidney transplantation. Further prospective, larger scale, controlled and multicenter cohort studies are needed to investigate the prevalence of hypophosphatemia in the early posttransplant period and its correlation with graft function.

Authors' Contribution

Study Conception: EIS; Study Design: EIS; Supervision: EIS; Funding: EIS; Materials: EIS; Data Collection and/or Processing: EIS; Statistical Analysis and/or Data Interpretation: EIS; Literature Review: EIS; Manuscript Preparation: EIS and Critical Review: EIS.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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