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LETTER TO THE EDITORS

Frequency and long-term outcomes of post-transplant hypophosphatemia after kidney transplantation

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Dear Sirs,

High frequencies (40–90%) of hypophosphatemia in the first month after successful kidney transplantation have been reported [1–6]. The consequence of hypophosphatemia and even its frequency beyond the first year are less known; in particular, data on long-term outcomes of this frequent laboratory abnormality are sparse, inconsistent, and based on studies mainly focussing on hyperphosphatemia [2–6]. Today, it is still debatable whether or not a low phosphate level is an independent risk factor for any adverse outcome, or just a marker of other causes. We therefore investigated the prevalence and natural course of post-transplant hypophosphatemia in our centre. Its relationship with long-term outcomes and associated risk factors were then explored.

All kidney-only adult (≥18 years at transplant) patients transplanted during 1 January 2000 to 31 December 2010 with >6 months follow-up were included. Demographics, pre- and post-transplant creatinine, bone mineral parameters as well as clinical data including death and graft failure information were completely recorded in our transplant database [7,8]. Patients were grouped into low (<0.8), normal (0.8–1.5) and high (>1.5 mmol/l) phosphate groups based on their 6-month phosphate levels. End of observation date is 15 October 2011.

In the 776 qualified subjects, there were 279 (36.1%) patients with low phosphate at 6-month (0.69 ± 0.08 mmol/l), 7 (1%) were <0.5 mmol/l. They had more male (67.7% vs. 57.5% and 58.8% in normal and high phosphate group, $P = 0.003$), received organs from younger donor (50.8 ± 14.9 vs. 53.7 ± 15, 53 ± 16.3 year-old in normal and high phosphate group, $P = 0.01$). Normal phosphate group was slightly older (50.4 ± 14.9, vs. 48.2 ± 13.6, 46.3 ± 16.5 year-old in low and high phosphate group, $P = 0.04$). Other clinical features, including dialysis duration, body mass index , donor type, initial immunosuppression were the same. Twenty-five to 30% transplant patients remained hypophosphatemic for up to 10 years. Although their phosphate levels improved later (0.76 ± 0.14, 0.8 ± 0.18, 0.84 ± 0.23, 0.89 ± 0.29 mmol/l at 1-, 3-, 5- and 10-year, $P < 0.05$ comparing with 6-month), they stayed significantly lower for at least 5 years compared with normal phosphate patients (1 ± 0.16, 1.02 ± 0.22, 1.05 ± 0.24, 1.02 ± 0.25 mmol/l at 1-, 3-, 5-year, respectively, $P < 0.05$). Meanwhile, low phosphate group exhibited higher eGFR (7–10 ml/min higher than normal phosphate group at 1-, 3-, 5-year, $P < 0.05$). They also had higher serum calcium, lower Ca ×phosphate product and higher calcitriol levels. No difference in parathyroid hormone (PTH) levels. The more favourable bone-mineral metabolic profile likely reflected better allograft function.

Outcomes examined included overall patient mortality, death-censored graft survival and graft survival. High-phosphate group (17 cases) had significantly worse outcomes (time to death 8.3 ± 1.2 years, time to death-censored graft failure 6.9 ± 1 years, to graft failure 5.7 ± 1 years, $P < 0.05$ for all) compared with low- and normal-phosphate group. They were excluded from further comparison. Results of univariate and multivariate Cox regression analysis were summarized in Table 1. In univariate analysis, low phosphate group had better graft survival (time to event: 10.3 ± 0.3 for low phosphate group, 9.0 ± 0.2 years for normal phosphate group, $P < 0.001$) and death-censored graft survival (time to event: 11.1 ± 0.2 for low phosphate group, 10.1 ± 0.2 years for normal phosphate group, $P = 0.004$). Advantages of low phosphate group over normal phosphate group were only present when eGFR was <60 ml/min (191 cases in low and 381 cases in normal phosphate group). When adjusted by other co-factors separately, the association between low phosphate and less death-censored graft failure was attenuated only when eGFR was introduced. None of the co-factors analysed offset the association between low phosphate group and improved overall graft survival.

We observed significant effects of hypophosphatemia at month 6 on all outcomes in univariate analysis. In multivariate analysis, it remained a major factor for graft survival, along with eGFR, however not for mortality or death-censored graft survival. The reason is unclear. Both

Table 1. Estimates of confounding predictors* of long-term outcomes using Cox proportional hazards model.

	Univariate		Multivariate	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Parameters for all-cause mortality				
Phosphate at 6 m, normal versus low	1.82 (1.11–2.99)	0.017	–	NS
Age at transplantation, older versus younger	4.85 (3.07–7.67)	<0.001	3.88 (2.23–6.74)	<0.001
Donor Type, deceased versus living donor	2.99 (1.68–5.36)	<0.001	–	NS
Donor Age, older versus younger	2.53 (1.67–3.83)	<0.001	1.66 (1.03–2.67)	0.039
eGFR at 6-month, < vs. >33.19 ml/min†	3.51 (2.02–6.10)	<0.001	2.37 (1.26–4.45)	0.007
Parameters for graft failure, death-censored				
Phosphate at 6 m, normal versus low	2.25 (1.28–3.95)	0.004	–	NS
Donor Type, deceased versus living donor	2.77 (1.57–4.89)	<0.001	1.94 (1.06–3.55)	0.033
Donor Age, older versus younger	1.59 (1.06–2.39)	0.025	–	NS
eGFR at 6-month, < vs. >33.19 ml/min	8.02 (4.78–3.46)	<0.001	5.51(3.02–10.06)	<0.001
Phosphate Supplement (non user versus user)	2.61 (1.45–4.68)	0.001	–	NS
Parameters for graft failure, non death-censored				
Phosphate at 6 m, normal versus low	2.00 (1.35–2.98)	0.001	1.63 (1.06–2.49)	0.025
Age at transplantation, older versus younger	1.89 (1.40–2.55)	<0.001	–	NS
Donor Type, deceased versus living donor	3.05 (1.97–4.73)	<0.001	2.21 (1.37–3.59)	0.001
Donor Age, older versus younger	1.91 (1.41–2.61)	<0.001	1.55 (1.08–2.21)	0.017
eGFR at 6-month,< vs. >33.19 ml/min	5.63 (3.71–8.56)	<0.001	3.95 (2.42–6.44)	<0.001

*Putative risk factors studied used for univariate analysis include gender, age, donor type and age, body mass index and phosphate supplement use. The following laboratory parameters were transformed from continuous variables into categorical variables: calcium and albumin-corrected calcium, transformed into <2.2, 2.2–2.6 and >2.6 mmol/l groups; calcium × phosphate product, <4 and >4; PTH, <6.8, 6.8–50 and >50 pmol/l; calcidiol, <12, 12–40, 40–75 and >75 nmol/l; calcitriol into its quartiles. Only those of which with significant association ($P < 0.2$) in univariate analysis were then entered into multivariate analysis.

†Value is the threshold to predict low and normal phosphate.

NS, nonsignificant.

age and donor age differed in these groups and both were important factors for mortality and graft survival. In addition, it likely indicates that hypophosphatemia itself is not strong enough to be an independent risk factor for these outcomes. Given the fact that effects of hypophosphatemia were only evident when allograft function was relatively compromised, and they were eliminated when eGFR was introduced, it is reasonable to postulate that hypophophatemia is mainly an indicator for excellent kidney function rather than having direct favourable effects on long-term outcomes. Allograft function is most likely the crucial role for long-term outcomes. This notion can be supported by the pathophysiology of post-transplant hypophosphatemia elucidated over the last decade [9].

Previous studies on the course of post-transplant hypophosphatemia mainly focus on the first year, and the prevalence beyond this first year is solely from cross-section studies [1,9]. There were only limited numbers of long-term survival study on hypophosphatemia [2,5]. We identified a high frequency of hypophosphatemia after transplantation that persists in about one-third of patients. Studies have linked low phosphate level predominantly to fibroblast growth factor 23 (FGF23) within the first year [1] and to PTH at later times [9]. Because of the retrospective nature of our study, FGF23 was not available and PTH data were incomplete. Further study, preferably prospective study, is needed to fully establish their association.

Limitations of our study include: It is a retrospective study not designed to explore the risk factors of hypophosphatemia or survival. FGF23 was not measured, and PTH and Vitamin D profile, and some important clinical data such as fracture, were incomplete in some patients. Medication effects, as well as comorbidity, were not investigated. However, our large sample size and the long and complete follow-up allow us to describe the natural course and address long-term outcomes suitably.

In conclusion, hypophosphatemia is a frequent and mostly neglected observation after renal transplantation. It persists for up to 10 years in 25–30% of transplant patients, with a more favourable bone-mineral metabolic profile and higher eGFR. It is associated with superior graft survival, however, most likely because of better allograft function rather than an independent factor for graft survival. Because of the retrospective nature of our study, additional study, especially prospective study, is required to validate our findings, to evaluate chronic complications of hypophosphatemia, and to assess the necessity and indication for treatment.

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Conflicts of interest

We declare that we have no conflict of interest related to this manuscript.

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References

1. Evenepoel P, Meijers BK, de Jonge H, *et al.* Recovery of hyperphosphatoninism and renal phosphorus wasting one year after successful renal transplantation. *Clin J Am Soc Nephrol* 2008; **3**: 1829.
2. Egbuna OI, Taylor JG, Bushinsky DA, Zand MS. Elevated calcium phosphate product after renal transplantation is a risk factor for graft failure. *Clin Transplant* 2007; **21**: 558.
3. Schaeffner ES, Fodinger M, Kramar R, Sunder-Plassmann G, Winkelmayer WC. Prognostic associations of serum calcium, phosphate and calcium phosphate concentration product with outcomes in kidney transplant recipients. *Transpl Int* 2007; **20**: 247.
4. Moore J, Tomson CR, Tessa Savage M, Borrows R, Ferro CJ. Serum phosphate and calcium concentrations are associated with reduced patient survival following kidney transplantation. *Clin Transplant* 2011; **25**: 406.
5. Stevens KK, Morgan IR, Patel RK, *et al.* Serum phosphate and outcome at one year after deceased donor renal transplantation. *Clin Transplant* 2011; **25**: E199.
6. Sampaio MS, Molnar MZ, Kovesdy CP, *et al.* Association of pretransplant serum phosphorus with posttransplant outcomes. *Clin J Am Soc Nephrol* 2011; **6**: 2712.
7. Glander P, Budde K, Schmidt D, *et al.* The 'blood group O problem' in kidney transplantation–time to change? *Nephrol Dial Transplant* 2010; **25**: 1998.
8. Larsson T, Nisbeth U, Ljunggren O, Juppner H, Jonsson KB. Circulating concentration of FGF-23 increases as renal function declines in patients with chronic kidney disease, but does not change in response to variation in phosphate intake in healthy volunteers. *Kidney Int* 2003; **64**: 2272.
9. Sirilak S, Chatsrisak K, Ingsathit A, *et al.* Renal phosphate loss in long-term kidney transplantation. *Clin J Am Soc Nephrol* 2011; **7**: 323.

