Associations of Fibroblast Growth Factor 23 with Parameters of Phosphate Metabolism in Incident Peritoneal Dialysis Patients

Disorders of phosphate metabolism are common complications in dialyzed patients, and control of serum phosphorus seems to be a critical factor in the survival of these patients. In several studies, a tight association has been observed between elevated serum phosphorus and mortality (1,2).

Regulation of phosphate homeostasis in chronic kidney disease (CKD) is controlled by a variety of factors, such as phosphate loading and serum calcium, vitamin D and parathyroid hormone (PTH). In peritoneal dialysis (PD), elimination of phosphate depends on peritoneal and renal phosphate clearance [the latter clearance depending on residual renal function (RRF)]. Recently, high serum levels of fibroblast growth factor 23 (FGF-23) have been regarded as independent factor associated with morbidity and mortality in dialyzed patients (3–6). In patients with CKD, circulating FGF-23 gradually increases with declining renal function. Isakova *et al.* (7) suggested that FGF-23 might be a sensitive early biomarker of disordered phosphorus metabolism in patients with CKD and a normal phosphate level, because FGF-23 increases earlier than either phosphate or PTH. However, the clinical significance of FGF-23 measurement in PD patients has not yet been fully established.

A recent study of ours (8) suggests that serum phosphate may be associated with peritoneal membrane transport in incident PD patients. The aim of the present study, conducted in a larger cohort of subjects, was to more thoroughly evaluate associations between regulators of phosphate metabolism (including FGF-23) and phosphate concentrations and clearances at the onset of PD.

METHODS

At the Peritoneal Dialysis Center, Department of Nephrology, Transplantology and Internal Medicine, Szczecin, Poland, 50 patients were started on continuous ambulatory PD using 4 daily exchanges of 1.5 – 2 L glucose-based dialysate with a calcium concentration of 1.25 mmol/L (Baxter Healthcare SA, Castlebar, Ireland). All patients gave written informed consent, and the study was approved by the local bioethics committee. Peritoneal and renal clearances of creatinine and phosphorus were calculated by means of direct determination from dialysis fluids, urine, and serum. Serum levels of FGF-23 were determined using a sandwich enzyme-linked immunosorbent assay (Human FGF-23 ELISA Kit: Millipore Corporation, Bedford, MA, USA).

Table 1 presents the main characteristics of the study group. The causes of end-stage renal disease were diabetes ($n = 6$), glomerulonephritis ($n = 12$), hypertension ($n = 10$), chronic pyelonephritis ($n = 3$), other ($n = 10$), and unknown ($n = 9$).

The Spearman rank correlation coefficient (R_s) was used to measure associations between quantitative variables. The Mann–Whitney test was used to compare values between groups. A general linear model was used for the multivariate analysis. Variables with non-normal distributions (serum FGF-23 and phosphorus), as evidenced by a Shapiro–Wilks test, were transformed logarithmically

TABLE 1
Characteristics of the Study Population

Variable	Value
Patients (*n*)	50
Mean age (years)	45.6±16.9
Sex [*n* (%)]	
Men	28 (56)
Women	22 (44)
Use of [*n* (%)]	
Calcium phosphate binders	35 (70)
Alpha-calcidiol	36 (72)
RRF (mL/min/1.73 m^2)	9.3±4.7
Diuresis (mL/d)	1934±1110
Weekly phosphate clearance (L)	
Renal	66.9±43.2
Peritoneal	35.6±8.9
Weekly peritoneal CCr (L)	39.3±8.8
D/P creatinine in PET	0.66±0.12
Hemoglobin (mmol/L)	7.2±0.8
Hematocrit (%)	34.0±3.9
Serum concentration of	
Albumin (g/L)	37.8±4.5
C-Reactive protein (mg/L)	9.5±14.7
Urea (mg/dL)	94.1±32.5
Creatinine (mg/dL)	5.5±2.3
Total calcium (mmol/L)	2.2±0.2
Phosphorus (mmol/L)	1.4±0.4
iPTH (pg/mL)	457±309
FGF-23 (pg/mL)	557±856

RRF = residual renal function; CCr = creatinine clearance; D/P = dialysate-to-plasma ratio; PET = peritoneal equilibration test; iPTH = intact parathyroid hormone; FGF-23 = fibroblast growth factor 23.

before the general linear model analysis. Values of *p* < 0.05 were considered statistically significant.

RESULTS

Hyperphosphatemia (that is, a phosphorus level > 1.8 mmol/L) was present in 28% of patients. Calcium and vitamin D supplementation were not significantly associated with serum calcium, phosphorus, PTH, or FGF-23.

We observed a strong positive correlation between serum phosphorus and FGF-23 (R_s = 0.54, *p* = 0.00085, Figure 1). Table 2 presents the associations of serum phosphorus, PTH, and FGF-23 with parameters of PD and RRF in patients at the onset of PD.

Renal phosphate clearance was strongly negatively correlated with serum phosphorus (R_s = –0.51, *p* = 0.003), but not with serum FGF-23 (R_s = –0.26, *p* = 0.19).
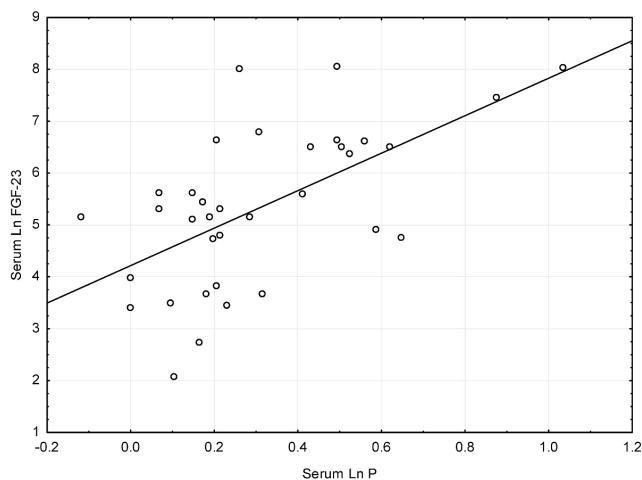

Figure 1 — Correlation between serum concentrations of phosphorus (P) and fibroblast growth factor 23 (FGF23) in incident PD patients. Both variables are logarithmically transformed (Ln).

TABLE 2
Associations[a] of Selected Serum Concentrations with Parameters of Peritoneal Dialysis and Residual Renal Function at Peritoneal Dialysis Onset

Parameter	Serum concentrations of			
	P (mmol/L)	FGF-23 (pg/mL)	iPTH (pg/mL)	Ca (mmol/L)
RRF (mL/min/ 1.73 m^2)	–0.43[b]	–0.42[c]	–0.03	0.27
Diuresis (mL/d)	–0.29[c]	–0.21	0.06	0.17
Weekly clearance (L)				
Renal, P	–0.51[b]	–0.26	–0.15	0.10
Peritoneal, P	–0.27	–0.06	0.12	–0.07
Peritoneal, Cr	0.17	0.29	0.05	–0.16
Serum P (mmol/L)	—	0.54[b]	0.29[c]	0.00

P = phosphate; FGF-23 = fibroblast growth factor 23; iPTH = intact parathyroid hormone; RRF = residual renal function; Cr = creatinine.
[a] As Spearman ρ coefficients.
[b] *p* < 0.01.
[c] *p* < 0.05.

Multivariate analysis using the log of serum FGF-23 as the dependent variable and the log of serum phosphate and the RRF as independent variables showed that, in patients at the onset of PD, a high phosphate concentration is an independent determinant of high serum FGF-23 (β = 0.53, *p* = 0.0028), independent of low RRF (β = –0.15, *p* = 0.36).

DISCUSSION

Of PD patients overall, 40% – 50% are estimated to have serum phosphate concentrations exceeding 1.8 mmol/L (9). In the present study, the prevalence of hyperphosphatemia was 28%, which is consistent with a study of 264 continuous ambulatory PD patients by Bernardo *et al.* (10) in which the prevalence reached 30% and, after 1 year of PD treatment, serum phosphate correlated negatively with RRF and renal phosphate clearance. We also observed negative correlations between serum phosphorus and renal phosphate clearance, which may underline the important role of RRF in phosphate metabolism at the beginning of PD therapy.

The main physiologic role of FGF-23 in healthy subjects is to increase urinary phosphate excretion to maintain stable levels of serum phosphate. The increase in FGF-23 starts at a very early stage of CKD in an attempt to stabilize serum phosphate as the number of intact nephrons declines. Several studies showed that increased serum FGF-23 was associated with increased cardiovascular risk and mortality in dialyzed patients (3,11). In a group of patients starting hemodialysis, Gutiérrez *et al.* (11) found a strong relationship between high serum FGF-23 and an increased risk for 1-year mortality. Interestingly, in that population, FGF-23 was a stronger predictor of mortality than serum phosphorus was. Other studies showed that serum FGF-23 is related to the prevalence of left ventricular hypertrophy in patients with CKD (12,13). In a study by Faul *et al.* (14), the authors reported that serum FGF-23 was independently associated with left ventricular hypertrophy in a large, racially diverse CKD cohort. Interestingly, studies on mice disclosed that the pathogenesis of left ventricular hypertrophy attributable to the action of FGF-23 had a klotho-independent mechanism.

In the PD patient population, data on FGF-23 are scarce. In a study by Isakova *et al.* (15), performed in 67 adult PD patients, the authors found that longer dialysis vintage ($R = 0.31$), lesser RRF ($R = –0.37$), and lower renal phosphate clearance ($R = –0.38$) were associated with higher levels of serum FGF-23. In a study performed in 35 incident PD patients, Viaene *et al.* (16) showed that declining renal function was inversely correlated with serum FGF-23. Those authors also observed a significant increase in serum phosphorus with the decline of RRF.

In the present study of incident PD patients, we found strong correlations between FGF-23 and RRF and between FGF-23 and serum phosphorus. Moreover, in multivariate analysis, we found that a high phosphorus concentration was a significant predictor of high FGF-23, independent of RRF. It seems possible that increased serum phosphorus is directly responsible for increased serum FGF-23, and that the influence of RRF is indirect (mediated by an increased phosphorus concentration). In our study, neither renal nor peritoneal phosphate clearance was associated with serum FGF-23, potentially suggesting that the influence of phosphate elimination on FGF-23 in incident PD patients is also indirect (mediated by serum phosphorus concentration).

To the best of our knowledge, we are the first to report the strong association between serum phosphorus and FGF-23, independent of RRF, in incident PD patients. Because increased serum FGF-23 can be independently associated with higher morbidity and mortality, it seems that, even in a group of incident PD patients without marked hyperphosphatemia, control of serum phosphate may bring benefits and improve outcomes.

CONCLUSIONS

Our study highlights the strong positive association between serum phosphorus and FGF-23 in patients at the start of PD therapy. This relationship is independent of RRF. Moreover, renal and peritoneal phosphate elimination are not associated with serum FGF-23. Because, by itself, increased FGF-23 may be associated with increased morbidity, further studies of FGF-23 as a potential target for clinical intervention are awaited.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

Edyta Golembiewska[1]*
Krzysztof Safranow[2]
Joanna Kabat–Koperska[1]
Kazimierz Ciechanowski[1]
Joanna Bober[3]
Anna Bogacka[4]

Department of Nephrology, Transplantology and Internal Medicine[1]
Departments of Biochemistry and Medical Chemistry[2]
Department of Medical Chemistry[3]
Pomeranian Medical University
Department of Human Nutrition[4]
West Pomeranian University of Technology
Szczecin, Poland

*email: irys@pum.edu.pl

REFERENCES

1. Tentori F, Blayney MJ, Albert JM, Gillespie BW, Kerr PG, Bommer J, et al. Mortality risk for dialysis patients with different levels of serum calcium, phosphorus and PTH: the Dialysis Outcomes and Practice Patterns Study. *Am J Kidney Dis* 2008; 52:519–30.

2. Kang SH, Cho KH, Park JW, Yoon KW, Do JY. Risk factors for mortality in stable peritoneal dialysis patients. *Ren Fail* 2012; 34:149–54.

3. Jean G, Terrat JC, Vanel T, Hurot JM, Lorriaux C, Mayor B, et al. High levels of serum fibroblast growth factor (FGF)-23 are associated with increasing mortality in long haemodialysis patients. *Nephrol Dial Transplant* 2009; 24:2792–6.

4. Stompór T. An overview of the pathophysiology of vascular calcification in chronic kidney disease. *Perit Dial Int* 2007; 27(Suppl 2):S215–22.

5. Srivaths PR, Goldstein SL, Silverstein DM, Krishnamurthy R, Brewer ED. Elevated FGF 23 and phosphorus are associated with coronary calcification in hemodialysis patients. *Pediatr Nephrol* 2011; 26:945–51.

6. Olauson H, Qureshi AR, Miyamoto T, Bárány P, Heimbürger O, Lindholm B, et al. Relation between serum fibroblast growth factor-23 level and mortality in incident dialysis patients: are gender and cardiovascular disease confounding the relationship? *Nephrol Dial Transplant* 2010; 25:3033–8.

7. Isakova T, Wahl P, Vargas GS, Gutiérrez OM, Scialla J, Xie H, et al. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int* 2011; 79:1370–8.

8. Golembiewska E, Kabat–Koperska J, Safranow K, Ciechanowski K. Free water transport is associated with phosphorus control in patients at initiation of peritoneal dialysis. *Perit Dial Int* 2011; 31:685–7.

9. Badve SV, McCormick BB. Phosphate balance on peritoneal dialysis. *Perit Dial Int* 2008; 28(Suppl 2):S26–32.

10. Bernardo AP, Contesse SA, Bajo MA, Rodrigues A, Del Peso G, Ossorio M, et al. Peritoneal membrane phosphate transport status: a cornerstone in phosphate handling in peritoneal dialysis. *Clin J Am Soc Nephrol* 2011; 6:591–7.

11. Gutiérrez OM, Mannstadt M, Isakova T, Rauh–Hain JA, Tamez H, Shah A, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 2008; 359:584–92.

12. Hsu HJ, Wu MS. Fibroblast growth factor 23: a possible cause of left ventricular hypertrophy in hemodialysis patients. *Am J Med Sci* 2009; 337:116–22.

13. Isakova T. Fibroblast growth factor 23 and adverse clinical outcomes in chronic kidney disease. *Curr Opin Nephrol Hypertens* 2012; 21:334–40.

14. Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, et al. FGF23 induces left ventricular hypertrophy. *J Clin Invest* 2011; 121:4393–408.

15. Isakova T, Xie H, Barchi–Chung A, Vargas G, Sowden N, Houston J, et al. Fibroblast growth factor 23 in patients undergoing peritoneal dialysis. *Clin J Am Soc Nephrol* 2011; 6:2688–95.

16. Viaene L, Bammens B, Meijers BKI, Vanrenterghem Y, Vanderschueren D, Evenepoel P. Residual renal function is an independent determinant of serum FGF-23 levels in dialysis patients. *Nephrol Dial Transplant* 2012; 27:2017–22.