Fibroblast Growth Factor 23 in Patients Undergoing Peritoneal Dialysis

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Summary
Background and objectives Fibroblast growth factor 23 (FGF23) is an independent risk factor for mortality in patients with ESRD. Before FGF23 testing can be integrated into clinical practice of ESRD, further understanding of its determinants is needed.

Design, setting, participants, & measurements In a study of 67 adults undergoing peritoneal dialysis, we tested the hypothesis that longer dialysis vintage and lower residual renal function and renal phosphate clearance are associated with higher FGF23. We also compared the monthly variability of FGF23 versus parathyroid hormone (PTH) and serum phosphate.

Results In unadjusted analyses, FGF23 correlated with serum phosphate ($r = 0.66, P < 0.001$), residual renal function ($r = -0.37, P = 0.002$), dialysis vintage ($r = 0.31, P = 0.01$), and renal phosphate clearance ($r = -0.38, P = 0.008$). In adjusted analyses, absence of residual renal function and greater dialysis vintage associated with higher FGF23, independent of demographics, laboratory values, peritoneal dialysis modality and adequacy, and treatment with vitamin D analogs and phosphate binders. Urinary and dialysate FGF23 clearances were minimal. In three serial monthly measurements, within-subject variability accounted for only 10% of total FGF23 variability compared with 50% for PTH and 60% for serum phosphate.

Conclusions Increased serum phosphate, loss of residual renal function, longer dialysis vintage, and lower renal phosphate clearance are associated with elevated FGF23 levels in ESRD patients undergoing peritoneal dialysis. FGF23 may be a more stable marker of phosphate metabolism in ESRD than PTH or serum phosphate.

Introduction
Disordered phosphorus metabolism is a common complication of kidney disease that contributes to the development of arterial calcification, myocardial hypertrophy, and endothelial dysfunction (1–3). Multiple observational studies have reported an independent association between hyperphosphatemia and mortality in patients with chronic kidney disease (CKD) and in the general population (4–6). However, isolated serum phosphate levels provide an imprecise assessment of disordered phosphorus metabolism because serum phosphate levels exhibit circadian and postprandial excursions of up to 1.0 mg/dl (7,8). Similar diurnal fluctuations have been reported in patients undergoing dialysis (9). As a result, lower serum phosphate levels measured during daily nadirs can belie more severe derangements in overall phosphorus balance and thus, likely underestimate the actual risk attributable to disordered phosphorus metabolism. Translating observations of phosphate-related risk of cardiovascular disease and mortality into improved patient care requires more sensitive tools for risk stratification than the serum phosphate.

Emerging data suggest that combining serum phosphate levels with measurements of its primary hormonal regulator, fibroblast growth factor 23 (FGF23), may enhance assessment of phosphorus-related cardiovascular risk. FGF23 levels increase early in the course of CKD and help maintain normal serum phosphate levels despite reduced renal function (10). Unlike parathyroid hormone (PTH), which is also involved in regulating serum phosphate but which fluctuates diurnally, in the context of meals, and acutely in response to changes in serum calcium, FGF23 levels exhibit minimal circadian and postprandial variation even in CKD (8,11–13). Prospective studies found elevated FGF23 to independently associate with mortality in incident hemodialysis patients, kidney transplant recipients, CKD stage 2 to 4, and individuals with a history of coronary artery disease (14–17). Furthermore, when directly compared with phosphate and PTH, FGF23 was the strongest predic-
tor of adverse outcomes (14, 15, 17). These data highlight the potential of FGF23 as a sensitive biomarker to help clinicians detect the presence of disordered phosphorus metabolism and perhaps, to more effectively discriminate risk of related adverse outcomes.

Before FGF23 can transition from research tool to biomarker for use in mainstream management of patients with ESRD, determinants of its marked interindividual variation in ESRD must be characterized. FGF23 levels in this setting are often the highest encountered in clinical practice, and levels can range from 10- to 1000-fold above the normal range. Chronic peritoneal dialysis is preferable to hemodialysis as a model to study determinants of FGF23 levels in ESRD because it is a form of renal replacement therapy in which a steady state is achieved. In addition, patients undergoing peritoneal dialysis often maintain some amount of residual renal function that is systematically quantified on a quarterly basis as part of standard care. Therefore, we used the peritoneal dialysis model to test our hypotheses that FGF23 levels would be greater in patients with longer dialysis vintage, reduced or absent residual renal function, and lower phosphate clearance and that short-term serial FGF23 measurements would exhibit less variability within individual patients over time than contemporaneous measurements of phosphate or PTH.

Materials and Methods

Study Population
We studied 67 consecutive patients aged 18 years or older who had been undergoing chronic peritoneal dialysis (continuous ambulatory peritoneal dialysis [CAPD] or continuous cyclic peritoneal dialysis) for the treatment of ESRD for at least 3 months at three participating institutions: University of Miami, Massachusetts General Hospital, and Vanderbilt University Medical Center. All willing participants were included; there were no exclusion criteria. The study protocol was approved by the human research committee at each institution, and all participants provided written informed consent.

Procedures
The study consisted of three or more consecutive monthly visits, which coincided with routine follow-up visits at the participating peritoneal dialysis clinics. Dialysate calcium prescription remained unchanged, and use of active vitamin D analogs, cinacalcet, and oral phosphate binders remained the same during the 3-month study period. The only changes to therapy that took place were switches in phosphate binder class in a minority of patients. We collected blood samples at all visits, and during the quarterly visits when dialysis adequacy was measured, we collected urine and dialysate samples from the 24-hour collections. A subset of 29 patients completed a single 4-day food record to estimate average daily dietary intake of phosphorus as analyzed by Nutrition Data System for Research, developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, Minnesota (18).

Calculations
We measured parameters of dialysis adequacy, including weekly total, renal and peritoneal Kt/V, and creatinine clearance, using standard methods (19). We calculated normalized protein equivalent nitrogen appearance (nPNA) normalized to body weight (20). We analyzed renal creatinine clearance (in ml/min per 1.73 m²) as the measure of residual renal function. Presence of residual renal function was defined as renal creatinine clearance greater than zero. Anuric patients were defined as having zero residual renal function.

We quantified the daily phosphate removal by dialysis or urinary excretion (mg/d) as follows:

\[
\text{dialysate [or urine] phosphate (mg/d) } \times 24\text{-hour dialysate [or urine] volume (ml/d)} \times 0.01.
\]

Total daily phosphate removal equaled the sum of daily peritoneal and renal phosphate removal.

Peritoneal and renal phosphate clearances (L/d per 1.73 m²) were calculated as follows:

\[
\text{dialysate [or urine] phosphate (mg/d)/plasma phosphate (mg/d) } \times 24\text{-hour dialysate [or urine] volume (ml/d)} \times 0.001 \text{ (L/ml)} \times (1.73 \text{ m}^2 \text{ BSA}).
\]
Total phosphate clearance equaled the sum of peritoneal and renal phosphate clearance.

In the subset of 10 participants for whom dialysate and urine FGF23 levels were measured, we calculated peritoneal and renal FGF23 clearances (ml/min/1.73 m²) as follows:

\[
\text{dialysate [or urine] FGF23 (RU/ml)/plasma FGF23 (RU/ml)} \\
\times 24\text{-hour dialysate [or urine] volume (ml/d)} \\
\times 1/1440 \text{ (d/min)} \times (1.73 \text{ m}^2 \text{ BSA}).
\]

Statistical Analysis

We compared laboratory and clinical characteristics in patients with and without residual renal function using t test, Wilcoxon, or chi-squared tests, as appropriate. The distributions of FGF23, PTH, and dialysis vintage were right-skewed, requiring natural log (ln)-transformation. To assess the univariate relationships of serum phosphate, residual renal function, dialysis vintage, and phosphate clearance with lnFGF23, we examined scatter plots and Pearson’s correlations. To determine if these associations were independent of demographics, laboratory values, peritoneal dialysis modality (CAPD or continuous cyclic peritoneal dialysis) and adequacy (Kt/V), and use of active vitamin D and phosphate binders, we used separate linear regression models with lnFGF23 as the dependent variable and residual renal function (dichotomous variable) and dialysis vintage (naturally log-transformed) as primary predictors. Next, we examined the within-subject range of variation for serum phosphate, PTH, and FGF23. For each marker, we calculated the intraclass correlation from estimates of between-subject (\(\sigma^2_\text{B}\)) and within-subject variance (\(\sigma^2_\text{W}\)), derived from mixed linear models, using the following formula: \(\sigma^2_\text{W}/(\sigma^2_\text{B} + \sigma^2_\text{W})\) (21). P values <0.05 were considered significant. Analyses were performed with SAS 9.2 (SAS Institute, Cary, North Carolina).

Results

Demographic, Clinical, and Laboratory Characteristics by Residual Renal Function

The study population consisted of 67 patients with mean (±SD) age of 47 ± 14 years; 52% were men, 15% were black, and 51% were Hispanic. Hypertension and diabetes were present in 84% and 31% of participants, respectively. Active vitamin D and phosphate binders were being used by approximately 85% of participants. Residual renal function was present in 64% of participants, and the median dialysis vintage was 15 months. Differences in demographic, clinical, and laboratory characteristics between participants with (n = 43) and without (n = 24) residual renal function are shown in Table 1. Patients with residual renal function had lower dialysis vintage and serum phosphate levels and used phosphate binders less frequently than anuric patients. Dietary phosphorus intake estimates trended higher in the patients with residual renal function, and the nPNA was significantly higher in this group compared with anuric patients. Despite greater total phosphate removal, the median FGF23 levels were 3.7-fold higher in patients without compared with those with residual renal function. PTH levels and use of active vitamin D analogs did not differ significantly between the groups.

Associations of Residual Renal Function, Dialysis Vintage, and Phosphate Clearance with FGF23

In unadjusted analyses (Figure 1), lnFGF23 correlated with serum phosphate (\(r = 0.66, P < 0.001\)), residual renal function (\(r = -0.37, P = 0.002\)), and dialysis vintage (\(r = 0.31, P = 0.01\)). After adjusting for demographics, other mineral metabolites (serum albumin, calcium, phosphate, and PTH), dialysis adequacy (peritoneal dialysis Kt/V), peritoneal dialysis modality, and treatment with active vitamin D and phosphate binders, higher serum phosphate (\(\beta = 0.50, P < 0.001\)), absence of residual renal function (\(\beta = -0.89, P = 0.03\)), and longer dialysis vintage (\(\beta = 0.43, P = 0.002\)) remained independently associated with higher FGF23 levels. Similarly, the log-linear relationship between lnFGF23 (on a continuous scale) and residual renal function (\(\beta = -0.07, P = 0.02\)) persisted among those with residual renal function after multivariable adjustment. Moreover, inclusion of both residual renal function and dialysis vintage together in the same multivariable model demonstrated that each was significantly associated with lnFGF23 in patients with residual renal function.

To explore whether intensity of phosphate clearance associated with FGF23 levels, we examined univariate associations between residual renal function and FGF23 in patients with residual renal function. In anuric patients, we correlated peritoneal clearance with FGF23 levels. As shown in Figure 1D, lnFGF23 correlated inversely with residual phosphate clearance (\(r = -0.38, P = 0.008\)) in patients with residual renal function. This relationship persisted after adjustment for demographic, laboratory values, peritoneal dialysis modality and adequacy, and treatment with vitamin D and phosphate binders. In contrast, there was no significant relationship between peritoneal clearance and lnFGF23 in patients with (\(r = 0.02, P = 0.92\)) or without (\(r = -0.14, P = 0.53\)) residual renal function.

FGF23 Clearance

In a subset of 10 participants with residual renal function (average renal creatinine clearance of 6.6 ml/min per 1.73 m²) in whom we measured FGF23 levels in dialysate and urine, plasma FGF23 levels correlated strongly with urinary FGF23 (\(r = 0.92, P < 0.001\)) and to a lesser extent with dialysate FGF23 (\(r = 0.60, P = 0.06\)). The median (interquartile range) renal FGF23 clearance was 0.2 (0.1 to 0.3) ml/min. The median (interquartile range) peritoneal FGF23 clearance was 0.8 (0.5 to 1.8) ml/min.

Variability of FGF23 versus PTH and Phosphate

Forty-four participants had 3-month repeated measurements of FGF23, PTH, and phosphate, and we used these values to quantify the components of variation for each mineral metabolite. Total variation is composed of the within- and between-subject variation, with the former further subdivided into analytic variation, arising from measurement error, and true biologic variation. For the three repeated tests of each of the markers of mineral metabolism, we first examined the within-subject mean and range
of variation, rank-ordered by individual participants’ means (Figure 2). For FGF23 and PTH both the measured scale and ln-transformed values are shown. Compared with PTH and phosphate, the overall range of within-subject variation was less pronounced for FGF23, and only became substantial at the highest values above the threshold when serial dilutions were required, and likely introduced greater analytic variation (Figure 2A, shaded areas). Table 2 presents the sources of variation in the three analytes and their intraclass correlations (ICC), which quantify the percentage of total variation explained by between-subject variation. The remainder is explained by within-subject variation. A high ICC indicates that most of the observed variability in a given assay is explained by be-

<table>
<thead>
<tr>
<th>Table 1. Demographic, clinical, and laboratory characteristics by residual renal function</th>
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<td>With RRF (n = 43)</td>
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<tr>
<td>Demographics</td>
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<td>age (years)a</td>
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<td>male (%)</td>
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<td>polycystic kidney disease (%)</td>
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<td>other (%)</td>
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<td>24-hour urine volume (ml)c</td>
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<td>Peritoneal dialysis vintage (months)c</td>
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<td>Continuous cycling peritoneal dialysis (%)</td>
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<td>FGF23 (RU/ml)c</td>
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<td>PTH (pg/ml)c</td>
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<td>Indices of dialysis adequacy</td>
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<td>dialysate creatinine clearance (ml/min per 1.73 m²)d</td>
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<td>residual renal creatinine clearance (ml/min per 1.73 m²)n</td>
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<td>total creatinine clearance (ml/min per 1.73 m²)d</td>
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<td>Phosphate clearanced</td>
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<td>dialysate phosphate clearance (L/d per 1.73 m²)c</td>
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<td>residual renal phosphate clearance (L/d per 1.73 m²)c</td>
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<td>total phosphate clearance (L/d per 1.73 m²)c</td>
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<tr>
<td>renal daily phosphate removal (mg/d)c</td>
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<td>nPNA (g/kg per day)a</td>
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<td>dietary phosphate (mg/d)c</td>
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<tr>
<td>phosphate binder use (%)</td>
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<td>active vitamin D use (%)</td>
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</table>

RRF, residual renal function; FGF23, fibroblast growth factor 23; RU, reference units; PTH, parathyroid hormone; nPNA, normalized protein equivalent nitrogen appearance.

a Values are expressed as mean ± SD.

b Calculated as weight in kilograms divided by height in meters squared (kg/m²).

c Values are medians with interquartile range in parentheses. —, not available.

d Phosphate clearances were available in 40 participants (24 with and 16 without residual renal function). Dietary intake was available in 29 participants (21 with and eight without residual renal function).
between-subject variation, implying greater stability within individual patients upon repeated measurements over time. In contrast, a low ICC implies that the within-subject variation is high and that repeated measurements in the same individuals over time will yield more disparate results. The ICC for FGF23 was significantly higher (based on nonoverlapping 95% confidence intervals [CI]) than for either PTH or phosphate, indicating that among the three, FGF23 had the largest component of variability explained by between-subject variation and thus, the lowest within-subject variation of 10%. Moreover, when we repeated these analyses in participants in the highest quartiles of FGF23 and PTH values, we found that the ICC for FGF23 was 0.7 (95% CI: 0.3 to 0.9) and the ICC for PTH was 0.3 (95% CI: 0.2 to 0.5). This suggests that FGF23 measurements are more stable than PTH within-individuals even at the highest end of the spectrum of each.

**Discussion**

We confirm that FGF23 levels are markedly elevated in patients with ESRD and associate with hyperphosphatemia. The new findings of this study are that longer dialysis vintage and lower residual renal function and renal phosphate clearance are also important determinants of higher FGF23 levels. Interestingly, despite controversy surrounding what is the ideal FGF23 assay, FGF23 demonstrated significantly less within-subject variability over a 3-month period compared with contemporaneous PTH and phosphate measurements. This suggests that single measurements of FGF23 may provide a more accurate assessment of disordered phosphate metabolism than either marker currently in use clinically. When considered alongside reports of elevated FGF23 independently associating with increased risk of cardiovascular disease and mortality (14,22), these data lend further support in favor of using FGF23 testing as a stable biomarker of disordered phosphate metabolism.

Studies in patients with chronic kidney disease not yet on dialysis, transplant donors, and animal experiments all demonstrate that reduced kidney function is a leading determinant of FGF23 levels (23–25). Although data on FGF23 levels in patients undergoing peritoneal dialysis are limited (11,26,27), one report linked absence of residual renal function with higher FGF23 levels in children (26). We report similar findings in adults and extend this observation by showing that among those with residual renal function, there is a continuous relationship between higher FGF23 and lower residual renal function and that longer dialysis vintage also independently associates with higher FGF23. These relationships were independent of other classic regulators of FGF23, including serum phosphate and use of active vitamin D and phosphate binders. Thus, in addition to differences in serum phosphate, differences in dialysis vintage and residual renal function contribute to the heterogeneity in FGF23 in the dialysis population.

Prior reports suggest that enhanced total phosphate clearance driven by residual renal function (28,29) may reduce FGF23 secretion, leading to the lower FGF23 levels we observed in this group compared with the anuric patients. However, we found that the anuric patients had higher FGF23 levels but greater total daily phosphorus removal. We can speculate that more severe hyperphos-
phosphatemia in this group maintained the concentration gradient for phosphate removal that drove their higher peritoneal removal of phosphate. Additionally, greater convective removal of phosphate in the anuric group, whose ultrafiltration requirements are higher than in patients who continue to make urine, may have contributed to their greater peritoneal phosphate removal. Yet, the anuric group had higher FGF23 levels in the setting of greater phosphate removal and despite lower dietary phosphorus intake and greater use of phosphate binders. This discrepancy could be explained by a direct stimulatory effect of their more severe hyperphosphatemia or their greater net positive phosphate balance due to longer dialysis vintage. Balance studies are needed to measure differences in phosphate balance between patients with and without residual renal function and their relation to FGF23 and serum phosphate levels.

In addition to increased FGF23 production by bone (30), it has been proposed that accumulation of FGF23 due to decreased renal clearance is an important mechanism of elevated FGF23 levels in patients with chronic kidney disease (31). Our pilot data suggest otherwise. We found that FGF23 clearance by the kidney or peritoneal dialysis is minimal, only 4% to 5% of the corresponding clearances of
creatinine. Our findings are in agreement with the one previous report in the literature of simultaneous FGF23 measurements in the blood (110 RU/ml) and urine (87.6 RU/ml) from a healthy volunteer (11). Assuming a urine volume of 2 L/d, the healthy individual’s FGF23 clearance was approximately 1.1 ml/min, which is in a comparably low range that we observed in patients with ESRD (median renal FGF23 clearance, 0.2 ml/min; median total FGF23 clearance, 1.2 ml/min). These data suggest that differences in FGF23 clearance, in its purest definition, contribute negligibly to FGF23 levels in health and in CKD. Alternatively, CKD could contribute to FGF23 “accumulation” through reduced cellular uptake, impaired proteolytic degradation, or aberrant processing of intact FGF23 in renal tubular cells, as has been described for other peptide hormones (32). Interestingly, a prior report showed that both the intact FGF23 and its C-terminal fragments were detected in the urine of dialysis patients with residual renal function (11). Additional studies are needed to identify mechanisms of FGF23 degradation and how these are affected by kidney disease.

Strengths of our study include an ethnically diverse population of patients receiving peritoneal dialysis across three academic centers in the United States, quantification of residual renal function and peritoneal and renal phosphate and FGF23 clearance, and availability of 3-month serial measurements of mineral metabolism markers. However, our study also has limitations. We were not able to study longitudinal changes in residual renal function and their association with FGF23 over longer durations, and our ascertainment of residual renal function relied on renal creatinine clearance, which may have overestimated the values due to tubular secretion of creatinine. Our assessment of dietary intake was limited to use of 4-day food records that provide only an estimate of short-term intake, and we were unable to study the components of phosphate balance antecedent to our evaluation. Finally, we did not take into account peritoneal membrane characteristics that were recently noted to play a role in peritoneal phosphate clearance (33).

Ideally, a clinically useful biomarker provides prognostic utility for outcomes of interest, is easily and reproducibly measured, and manifests minimal variability diurnally and longitudinally. These appear to be characteristics of FGF23. In addition to associating with outcomes and varying minimally across the day and with relation to meals, we report minimal within-subject variability during

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Between-Subject $\sigma^2_{B}$</th>
<th>Within-Subject $\sigma^2_{W}$</th>
<th>Total Variance $\sigma^2_{B} + \sigma^2_{W}$</th>
<th>ICC Estimate$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>lnFGF23</td>
<td>8.2</td>
<td>2.5 (0.4)</td>
<td>0.3 (0.03)</td>
<td>2.8 (0.4)</td>
<td>0.9 (0.82 to 0.95)</td>
</tr>
<tr>
<td>lnPTH</td>
<td>5.6</td>
<td>0.4 (0.1)</td>
<td>0.5 (0.06)</td>
<td>0.9 (0.1)</td>
<td>0.5 (0.32 to 0.60)</td>
</tr>
<tr>
<td>Phosphate</td>
<td>5.7</td>
<td>2.4 (0.5)</td>
<td>1.4 (0.2)</td>
<td>3.8 (0.5)</td>
<td>0.6 (0.39 to 0.76)</td>
</tr>
</tbody>
</table>

FGF23, fibroblast growth factor 23; PTH, parathyroid hormone; ICC, intraclass correlation.

$^a$ Values are expressed as mean with SEM in parentheses.

$^b$ Values in parentheses are 95% confidence intervals. The ICC was calculated from estimates of between-subject ($\sigma^2_{B}$) and within-subject variance ($\sigma^2_{W}$), derived from mixed linear models, using the following formula: $\sigma^2_{B}/(\sigma^2_{B} + \sigma^2_{W})$. 3-month serial measurements of FGF23. Indeed, the variability was higher only in participants with the highest values when 1:100 or greater dilutions were required, which likely introduced significant (human) measurement error more than true biologic scatter. Despite this variation at the high range, FGF23 demonstrated significantly less overall within-subject variation than serum phosphate or PTH, which have known circadian patterns (7,8,13). In support of our findings, a recent report estimated that 26 PTH measurements would be needed to accurately estimate an individual hemodialysis patient’s true homeostatic set point for PTH (34). Although comparable studies are needed in peritoneal dialysis patients, these results suggest that FGF23 is a more stable marker of phosphate metabolism than PTH or phosphate, which could help explain its stronger association with outcomes and support the further development of FGF23 testing for clinical practice.

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Disclosures
None.

References
5. Block GA, Hulbert-Shearon TE, Levin NW, Port FK: Association of serum phosphorus and calcium × phosphate product

FGF23 and Peritoneal Dialysis, Isakova et al. 2695

with mortality risk in chronic hemodialysis patients: A na-

Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger
SL, Young B, Sherrard DJ, Andress DL: Serum phosphate lev-
eels and mortality risk among people with chronic kidney disease.
J Am Soc Nephrol 16: 520–528, 2005

Markowitz M, Rotkin L, Rosen JF: Circadian rhythms of bone

Isakova T, Guthrie MD, Shah A, Castaldo L, Holmes J, Lee H,
Wolf M: Postprandial mineral metabolism and secondary hy-
perparathyroidism in early CKD. J Am Soc Nephrol 19: 615–
623, 2008

Ring T, Sanden AK, Hansen HH, Halkier P, Nielsen C, Fog L:
Ultradian variation in serum phosphate concentration in pa-
tients on haemodialysis. Nephrol Dial Transplant 10: 59–63,
1995

Isakova T, Wahl P, Vargas GS, Gutierrez OM, Scialla J, Xie
H, Appleby D, Nessel L, Bellowich K, Chen J, Hamm L, Gade-
egbeku C, Horwitz E, Townsends RR, Anderson CA, Lash JP, 
Hsu CY, Leonard MB, Wolf M: Fibroblast growth factor 23 is
elevated before parathyroid hormone and phosphate in chronic

Larsson T, Nisbeth U, Ljunggren O, Juppner H, Jonsson KB:
Circulating concentration of FGF-23 increases as renal func-
tion declines in patients with chronic kidney disease, but
does not change in response to variation in phosphate intake

Carpenter TO, Insogna KL, Zhang JH, Ellis B, Nieman S, 
Parker BD, Schurgers LJ, Brandenburg VM, Christenson RH,
Pereira RC, Juppner H, Azucena-Serrano CE, Yadin O, Sa-
lusky IB, Gomes T, Jaffe EA, de Jong M, de Vries PC, 
Kuhlmann MK: Phosphate elimination in modalities of hemo-
2796, 2009

Gutierrez O, Isakova T, Rhee E, Shah A, Holmes J, Collerone
G, Juppner H, Wolf M: Fibroblast growth factor-23 miti-
গত hyperphosphatemia but accentuates calcitriol deficien-
2005

Westerberg PA, Ljunggren O, Larsson TE, Wadstrom J, Linde
T: Fibroblast growth factor-23 and mineral metabolism after
4071, 2010

Hasegawa H, Nagano N, Urakawa I, Yamazaki Y, Iijima K,
Fujita T, Yamashita T, Fukumoto S, Shimada T: Direct evi-
dence for a causative role of FGF23 in the abnormal renal
phosphate handling and vitamin D metabolism in rats with
early-stage chronic kidney disease. Kidney Int 78: 975–980,
2010

Wesseling-Perry K, Pereira RC, Wang H, Elashof RM, Sahe-
y S, Gales B, Juppner H, Salusky IB: Relationship between
plasma fibroblast growth factor 23 concentration and bone
mineralization in children with renal failure on peritoneal

Shimada T, Urakawa L, Isakova T, Yamazaki Y, Epstein M,
Wesseling-Perry K, Wolf M, Salusky IB, Juppner H: Circulat-
ing fibroblast growth factor 23 in patients with end-stage re-
nal disease treated by peritoneal dialysis is intact and biologi-

Wang AY, Woo J, Sea MM, Law MC, Lui SF, Li PK: Hyper-
phosphatemia in Chinese peritoneal dialysis patients with
and without residual kidney function: What are the implica-

Kuhlmann MK: Phosphate elimination in modalities of hemo-
dialysis and peritoneal dialysis. Blood Purif 29: 137–144,
2010

Pereira RC, Juppner H, Azucena-Serrano CE, Yadon O, Sa-
lusky IB, Wesseling-Perry K: Patterns of FGF-23, DMP1, and
MEPE expression in patients with chronic kidney disease.
Bone 45: 1161–1168, 2009

Filler G, Liu D, Huang SH, Casier S, Chau LA, Madrenas J:
Impaired GFR is the most important determinant for FGF-23
437, 2011

Waldmann TA, Strober W, Mogieliicki RP: The renal han-
dling of low molecular weight proteins. II. Disorders of serum
protein catabolism in patients with tubular proteinuria, the
nephrotic syndrome, or uremia. J Clin Invest 51: 2162–2174,
1972

Bernardo AP, Contesse SA, Bajo MA, Rodrigues A, Del Peso
G, Ossorio M, Cabrita A, Selgas R: Peritoneal membrane
phosphate transport status: A cornerstone in phosphate han-
597, 2011

Gardham C, Stevens PE, Delaney MP, LeRoux M, Coleman
A, Lamb EJ: Variability of parathyroid hormone and other
markers of bone mineral metabolism in patients receiving

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