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Hyperphosphatemia with elevated serum PTH and FGF23, reduced 1,25(OH)₂D and normal FGF7 concentrations characterize patients with CKD

Kittrawee Kritmetapak^{1,2}, Louis Losbanos¹, Taylor E. Berent¹, Susan L. Ashrafzadeh-Kian³, Alicia Algeciras-Schimmich^{3,4}, Jolaine M. Hines⁵, Ravinder J. Singh⁴ and Rajiv Kumar^{1,6*}

Abstract

Background: Hyperphosphatemia confers adverse cardiovascular outcomes, and commonly occurs in late-stage CKD. Fibroblast growth factor 7 (FGF7) is a phosphaturic peptide which decreases renal phosphate transport *in vitro* and *in vivo*. Serum FGF7 concentrations are reduced in hyperphosphatemic patients with hypophosphatasia and are elevated in some hypophosphatemic patients with tumor-induced osteomalacia. No data, however, are available on whether circulating FGF7 concentrations increase to compensate for phosphate retention in CKD patients.

Methods: This was a cross-sectional study performed among 85 adult patients with varying estimated glomerular filtration rates (eGFR). We measured serum intact FGF7 (iFGF7) concentration using an iFGF7 immunoassay and determined its associated factors. Relationships between eGFR and mineral metabolism biomarkers [phosphate, iFGF7, iFGF23, parathyroid hormone (PTH), and 1,25-dihydroxyvitamin D (1,25(OH)₂D)] were explored.

Results: For eGFRs of ≥ 60 ($n = 31$), 45–59 ($n = 16$), 30–44 ($n = 11$), 15–29 ($n = 15$), and < 15 mL/min/1.73 m² ($n = 12$), median (IQR) iFGF7 concentrations were 46.1 (39.2–56.9), 43.1 (39.0–51.5), 47.3 (38.3–66.5), 47.7 (37.7–55.8), and 49.6 (42.5–65.6) pg/mL, respectively ($P = 0.62$). Significant increases in serum iFGF23, PTH, and phosphate were observed at eGFRs of < 33 (95 % CI, 26.40–40.05), < 29 (95 % CI, 22.51–35.36), and < 22 mL/min/1.73 m² (95 % CI, 19.25–25.51), respectively, while significant decreases in serum 1,25(OH)₂D were observed at an eGFR of < 52 mL/min/1.73 m² (95 % CI, 42.57–61.43). No significant correlation was found between serum iFGF7 and phosphate, iFGF23, PTH or 1,25(OH)₂D. In multivariable analyses, body mass index (per 5 kg/m² increase) was independently associated with the highest quartile of serum iFGF7 concentration (OR, 1.20; 95 % CI, 1.12–1.55).

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* Correspondence: rkumar@mayo.edu

¹Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic, 200 1st Street SW, MN 55905 Rochester, USA

⁶Department of Biochemistry and Molecular Biology, Mayo Clinic, MN, Rochester, USA

Full list of author information is available at the end of the article



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Conclusions: Compensatory decreases in circulating 1,25(OH)₂D and increases in circulating iFGF23 and PTH, but not iFGF7, facilitate normalization of serum phosphate concentration in early stages of CKD. Whether other circulating phosphaturic peptides change in response to phosphate retention in CKD patients deserves further study.

Keywords: Chronic kidney disease, Fibroblast growth factor, Parathyroid hormone, Phosphate, Vitamin D

Background

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is characterized by deranged metabolism of calcium, phosphate, parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and 1,25-dihydroxyvitamin D (1,25(OH)₂D).[1–3] In addition to changes in calciotropic and phosphotropic factors, CKD-MBD is frequently associated with bone abnormalities and vascular calcifications, which contribute to the substantial burden of cardiovascular disease in patients with CKD.[4] The complex pathophysiology of CKD and associated bone and mineral disorders involve a number of feedback loops between the kidneys, parathyroid glands, bones, intestine, and vasculature. These alterations occur early during the course of CKD before the onset of clinically detectable abnormalities in bone and vascular system. With progressive loss of kidney function, urinary phosphate excretion and serum phosphate concentration are initially maintained by reducing the proximal tubular reabsorption of filtered phosphate in the remaining functioning nephrons, an effect mediated mainly by compensatory increases in both circulating PTH and FGF23 concentrations. In addition to its phosphaturic effect, FGF23 also suppresses renal synthesis of 1,25(OH)₂D by inhibiting expression of the enzyme 1- α -hydroxylase (CYP27B1), while stimulating the catabolic enzyme 24-hydroxylase (CYP24A1). Hyperphosphatemia, however, is eventually observed in patients with advanced stages of CKD, when the estimated glomerular filtration rate (eGFR) declines below 30 mL/min/1.73 m². [5] It is not known whether other circulating phosphaturic factors (“phosphatonins”) increase as a result of reduced renal clearance or rise to compensate for phosphate retention in patients with CKD.

Fibroblast growth factor (FGF7), also known as heparin-binding growth factor 7 or keratinocyte growth factor, is a 28-kDa protein with phosphatonin-like activity,[6] which is normally expressed in keratinocytes and various epithelial cells.[7, 8] FGF7 prevents epithelial cell injury from reactive oxygen derivatives and promotes wound healing. Deletion of FGF7 in mice alters kidney morphogenesis, resulting in abnormally small ureteric buds and fewer nephrons.[9] FGF7 has been shown to be overexpressed in some patients with tumor-induced (oncogenic) osteomalacia, causing renal phosphate

wasting and refractory hypophosphatemia.[10, 11] Moreover, a recent study revealed that serum FGF7 concentrations in pediatric patients with hypophosphatasia and hyperphosphatemia were significantly lower than in control group (27.0 ± 7.7 versus 38.4 ± 3.0 pg/mL, $P < 0.0001$), and intravenous administration of recombinant FGF7 caused phosphaturia in rats, suggesting that FGF7 insufficiency could contribute to hyperphosphatemia in pediatric hypophosphatasia.[12].

There is no data available regarding serum FGF7 concentrations in patients with CKD. We hypothesized that the phosphatonin FGF7 might play a role in compensating for the elevation of serum phosphate concentrations in patients with CKD. Furthermore, FGF7 may be elevated in response to diminished renal clearance. Therefore, we performed a cross-sectional study to determine the relationship between serum intact FGF7 (iFGF7) concentration, eGFR, and associated factors in patients with a broad range of kidney function.

Methods

This cross-sectional study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Mayo Clinic Institutional Review Board. As we collected residual blood drawn for routine clinical laboratory tests and the study involved no more than minimal risk, the need for obtaining informed consent was waived. Non-identified information was used to protect patient data confidentiality. Serum samples were collected from 85 non-dialysis patients aged 18 years or older with varying eGFR at Mayo Clinic in Rochester, Minnesota, from September through November 2019. Patients were excluded when they had a known history of phosphate wasting disorders (e.g., tumor-induced osteomalacia, X-linked hypophosphatemic rickets, autosomal dominant hypophosphatemic rickets), hypophosphatasia, primary hyperparathyroidism, were being treated with activated forms of vitamin D (calcitriol or paricalcitol) or calcimimetics (cinacalcet or etelcalcetide), or were currently receiving renal replacement therapy (hemodialysis, peritoneal dialysis, or kidney transplant). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation was used to classify CKD severity (CKD1: eGFR ≥ 90; CKD2: eGFR 60–89; CKD3a: eGFR 45–59; CKD3b: eGFR 30–44;

CKD4: eGFR 15–29; and CKD5: eGFR < 15 mL/min/1.73 m²). Patient serum samples were stored at –80°C until analysis.

Laboratory parameters, including hemoglobin, fasting plasma glucose, blood urea nitrogen, serum creatinine, albumin, electrolytes, calcium, phosphate, and total alkaline phosphatase concentration, were measured using standard automated assays in the Central Clinical Laboratory at Mayo Clinic. Serum PTH concentrations were measured using a second-generation iPTH immunoassay and a Roche Cobas e411 analyzer (Roche Diagnostics, Mannheim, Germany). Serum 25(OH)D and 1,25(OH)₂D concentrations were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Serum iFGF7 and iFGF23 concentrations were measured using the recombinant human iFGF7 enzyme-linked immunosorbent assay (R&D Systems, MN, USA) and the human iFGF23 enzyme-linked immunosorbent assay (Eagle Biosciences, NH, USA), respectively. The inter- and intra-assay coefficients of variation (CV) were 6.0 and 3.3 % for the iFGF7 immunoassay, and less than 5 % for the iFGF23 immunoassay, respectively. The lower limits of detection for iFGF7 and iFGF23 immunoassays were 15 and 10 pg/mL, respectively.

Statistical analysis

Statistical analysis included computing (i) the frequency counts and percentages for the categorical variables and (ii) the means ± standard deviations (SD) or medians with interquartile ranges (IQ25 and IQ75) for the continuous variables. Continuous variables were tested for normality using a Shapiro-Wilk test. For non-normally distributed continuous variables, medians with interquartile ranges (IQ25 and IQ75) were presented. We examined interrelationships of measured serum analytes using nonlinear regression analysis. A segmented regression model was used to detect thresholds at which a statistically significant change was observed in the slope of serum analyte concentrations in relation to eGFR.[13] Univariate regression analyses were performed to determine the associations between serum iFGF7 concentrations and potential factors: age, sex, body mass index (BMI), eGFR, 24-hour urine protein, albumin-corrected serum calcium, serum phosphate, PTH, FGF23, and 1,25(OH)₂D concentrations. Only factors that had univariate associations of *P* values < 0.25 were further considered in subsequent multivariate models.[14] Lack of collinearity was confirmed by testing variance inflation factors. All tests were two-sided and *P* values < 0.05 were considered statistically significant. All statistical analysis was performed using STATA, version 14.0 (TX, USA).

Results

A cohort of 85 patients with a broad range of eGFR was recruited (Table 1). The mean (± SD) age was 58.2 ± 16.6 years, and 57.6 % of patients were female. The mean (± SD) eGFR was 53.9 ± 31.7 mL/min/1.73 m², the median (IQR) 24-hour urine protein was 347 (198–1,485) mg/24 h, and 28.2 % of patients had received a diagnosis of type 2 diabetes. A total of 17.6 % of patients had low serum 25(OH)D concentrations (< 30 ng/mL).

Changes in biomarkers of Mineral Metabolism across CKD stages

As eGFR declined, we observed a progressive increase of serum iFGF23, PTH, and phosphate concentrations and a progressive reduction in serum 1,25(OH)₂D concentrations. Interestingly, serum iFGF7 concentrations remained relatively unchanged (Figs. 1 and 2). There was no significant association between kidney function and albumin-corrected serum calcium, total alkaline phosphatase, or 25(OH)D concentrations.

Significant increases in serum concentrations of iFGF23, PTH, and phosphate were observed at eGFRs of < 33 (95 % CI, 26.40–40.05), < 29 (95 % CI, 22.51–35.36) and < 22 mL/min/1.73 m² (95 % CI, 19.25–25.51), respectively. Moreover, a significant decrease in serum 1,25(OH)₂D concentrations was observed at an eGFR of < 52 mL/min/1.73 m² (95 % CI, 42.57–61.43). We observed a positive correlation between serum phosphate and PTH concentrations ($R^2 = 0.5160$; $P < 0.01$; Fig. 3 a) and a positive correlation between serum phosphate and iFGF23 concentrations ($R^2 = 0.3679$; $P < 0.01$; Fig. 3b). Additionally, we observed a negative correlation between serum phosphate and 1,25(OH)₂D concentrations ($R^2 = 0.2602$; $P < 0.01$; Fig. 3 c) and a negative correlation between serum iFGF23 and 1,25(OH)₂D concentrations ($R^2 = 0.4088$; $P < 0.01$; Fig. 3d).

Serum concentration of iFGF7 in patients with CKD

The median (IQR) serum iFGF7 concentration was 46.2 (39.4–56.7) pg/mL and did not significantly differ across the stages of CKD. For eGFRs of ≥ 60, 45–59, 30–44, 15–29, and < 15 mL/min/1.73 m², median (IQ25–75) serum iFGF7 concentrations were 46.1 (39.2–56.9), 43.1 (39.0–51.5), 47.3 (38.3–66.5), 47.7 (37.7–55.8), and 49.6 (42.5–65.6) pg/mL, respectively ($P = 0.62$). There was no significant correlation between serum iFGF7 concentrations and serum phosphate, PTH, iFGF23, 25(OH)D, or 1,25(OH)₂D concentrations. We stratified patients by quartiles of serum iFGF7 concentration: 22 subjects were in the 1st quartile (serum iFGF7 < 39.4 pg/mL), 21 were

Table 1 Clinical characteristics of the study patients, according to stages of CKD

Characteristics	Estimated GFR (mL/min/1.73 m ²)				
	≥ 60 (n = 31)	45–59 (n = 16)	30–44 (n = 11)	15–29 (n = 15)	< 15 (n = 12)
Age (yr)	51.1 ± 17.2	60.2 ± 15.3	60.4 ± 14.9	63.6 ± 16.5	67.1 ± 12.0
Female sex (no. [%])	21 (67.7)	9 (56.3)	7 (63.6)	8 (53.3)	4 (33.3)
Diabetes (no. [%])	6 (19.4)	5 (31.3)	4 (36.4)	4 (26.7)	5 (41.7)
Calcium use (no. [%])	8 (25.8)	4 (25.0)	2 (18.2)	4 (26.7)	4 (33.3)
Cholecalciferol or ergocalciferol use (no. [%])	13 (41.9)	6 (37.5)	3 (27.3)	4 (26.7)	6 (50)
Body mass index (kg/m ²)	28.1 ± 6.0	26.7 ± 6.1	27.8 ± 5.7	29.5 ± 6.3	32.2 ± 9.2
Systolic blood pressure (mmHg)	120.9 ± 13.7	127.7 ± 16.8	122.6 ± 21.6	125.7 ± 11.7	135.5 ± 16.0
Hemoglobin (g/dL)	12.6 ± 1.4	11.9 ± 1.7	11.5 ± 1.0	11.0 ± 2.0	10.6 ± 1.2
Fasting plasma glucose (mg/dL)	109 ± 23	113 ± 32	109 ± 20	117 ± 30	124 ± 42
Blood urea nitrogen (mg/dL)	16.4 ± 4.6	21.3 ± 5.4	24.9 ± 7.4	44.5 ± 8.5	54.4 ± 14.4
Estimated GFR (mL/min/1.73 m ²)	88.1 ± 17.3	51.4 ± 4.8	37.1 ± 3.2	23.7 ± 4.4	12.8 ± 1.5
Serum sodium (mEq/L)	140.4 ± 2.9	140.8 ± 1.7	140.2 ± 2.5	140.5 ± 2.4	141.4 ± 2.8
Serum potassium (mEq/L)	4.2 ± 0.5	4.6 ± 0.4	4.4 ± 0.4	4.5 ± 0.6	4.6 ± 0.3
Serum chloride (mEq/L)	103.1 ± 3.0	103.9 ± 1.7	104.9 ± 4.6	104.3 ± 3.1	103.7 ± 5.8
Serum bicarbonate (mEq/L)	24.5 ± 2.0	24.0 ± 1.4	22.1 ± 2.5	23.7 ± 4.4	21.9 ± 2.9
Corrected serum calcium (mg/dL) ^a	9.5 ± 0.5	9.4 ± 0.4	9.4 ± 0.5	9.4 ± 0.4	9.3 ± 0.5
Serum phosphate (mg/dL)	3.3 ± 0.4	3.3 ± 0.7	3.5 ± 0.6	4.0 ± 0.6	4.7 ± 0.3
Serum alkaline phosphatase (U/L) ^b	85 (61–100)	58 (52–91)	64 (53–80)	104 (70–112)	92 (76–116)
24-hour urine protein (mg/day) ^b	227 (147–377)	185 (135–410)	287 (252–502)	611 (347–2,327)	2561 (1554–4208)
Serum parathyroid hormone (pg/mL) ^b	63 (47–85)	66 (45–83)	72 (46–93)	115 (92–168)	246 (143–393)
Serum 25(OH)D (ng/mL)	38.8 ± 11.9	49.9 ± 12.3	37.1 ± 11.9	42.2 ± 13.0	41.8 ± 15.7
Serum 1,25(OH) ₂ D (pg/mL)	41.5 ± 12.7	33.5 ± 12.5	29.8 ± 11.6	21.7 ± 8.4	15.6 ± 1.8
Serum intact FGF7 (pg/mL) ^b	46.1 (39.2–56.9)	43.1 (39.0–51.5)	47.3 (38.3–66.5)	47.7 (37.7–55.8)	49.6 (42.5–65.6)
Serum intact FGF23 (pg/mL) ^b	41.9 (33.0–52.7)	56.4 (46.9–60.2)	62.9 (50.9–79.3)	117.5 (88.4–156.6)	415.9 (278.3–500.9)

For continuous variables, mean ± SD; for categorical variables, n (%); unless otherwise specified

^aCorrected serum calcium (mg/dL) = measured total calcium (mg/dL) + 0.8(4.0 – serum albumin (g/dL))

^bShown as median (interquartile range, 25–75 %)

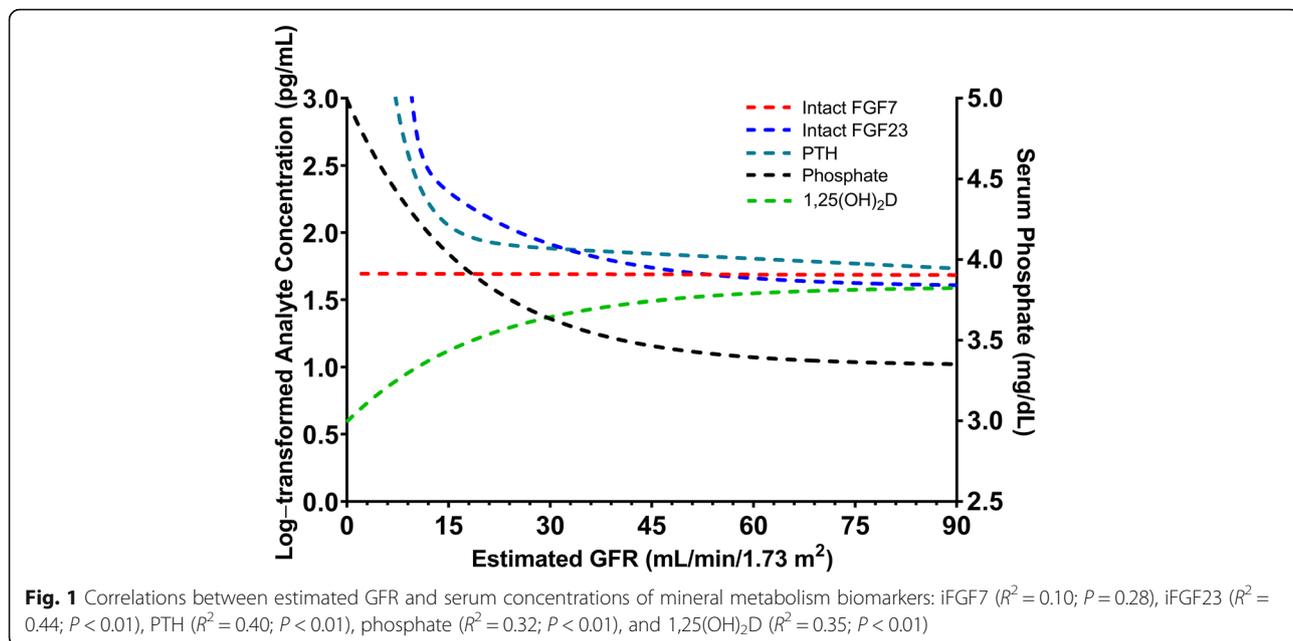
in the 2nd quartile ($39.4 \leq$ serum iFGF7 < 46.4 pg/mL), 21 were in the 3rd quartile ($46.4 \leq$ serum iFGF7 < 56.7 pg/mL), and 21 were in the 4th quartile (serum iFGF7 \geq 56.7 pg/mL). Multiple logistic regression analysis that adjusted for sex, age, BMI, eGFR, serum phosphate, and 1,25(OH)₂D concentrations revealed that higher BMI was independently associated with the highest quartile of serum iFGF7 concentration (OR per 5 kg/m² increase in BMI, 1.20; 95 % CI, 1.12–1.55; Table 2).

Discussion

In this cross-sectional study of non-dialysis patients with varying degrees of kidney dysfunction, we show, for the first time, that serum concentrations of the phosphatonin iFGF7 are not significantly altered across the stages of CKD. Based on multiple logistic regression analyses, we found that elevated serum iFGF7 concentrations are

associated with higher BMI. This research confirms previous findings that a decrease in serum 1,25(OH)₂D concentrations and an increase in serum iFGF23 concentrations occur in early stages of CKD, whereas increases in serum PTH and phosphate concentrations are observed at later stages of CKD.

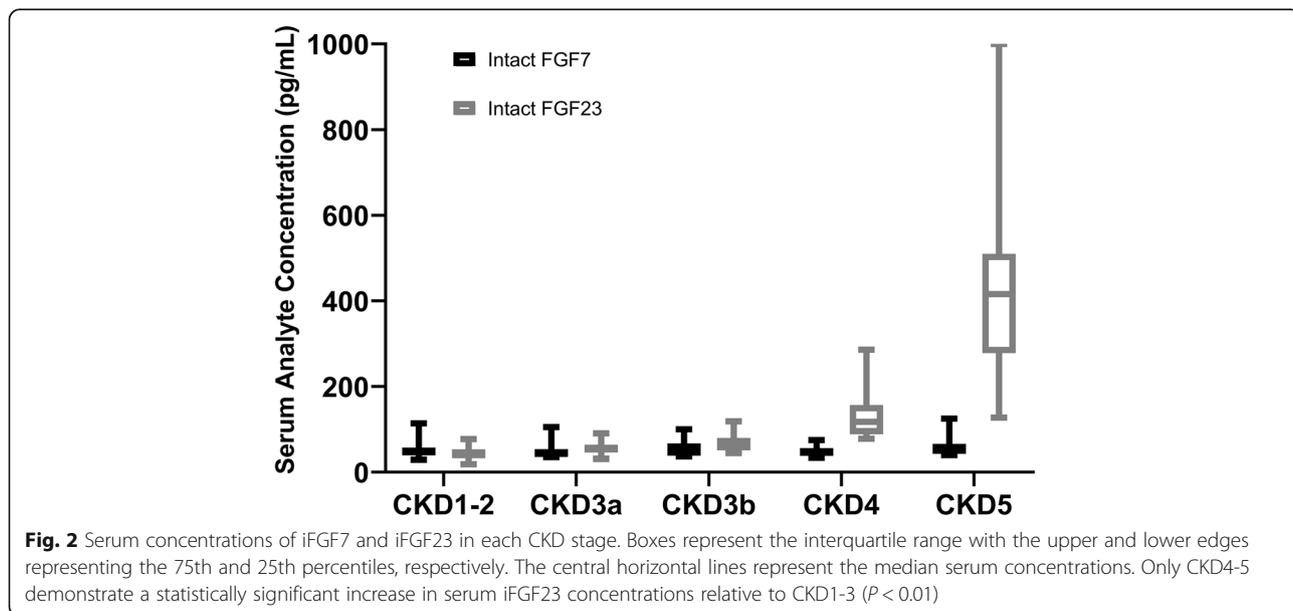
Fibroblast growth factor (FGF7), also known as heparin-binding growth factor 7 or keratinocyte growth factor, is a 28-kDa protein of the FGF family which is highly expressed in various epithelial cells including keratinocytes. FGF7 acts as an autocrine or paracrine growth factor by activating the FGFR2b receptor on epithelial cell membranes.[15, 16] FGF7 plays a role in morphogenesis (e.g., kidney development), angiogenesis, tissue repair, and tumorigenesis.[9, 17–19] FGF7 expression is also upregulated in kidney tissues from patients with autosomal dominant polycystic kidney disease.[20] Several reports demonstrate the phosphatonin-like

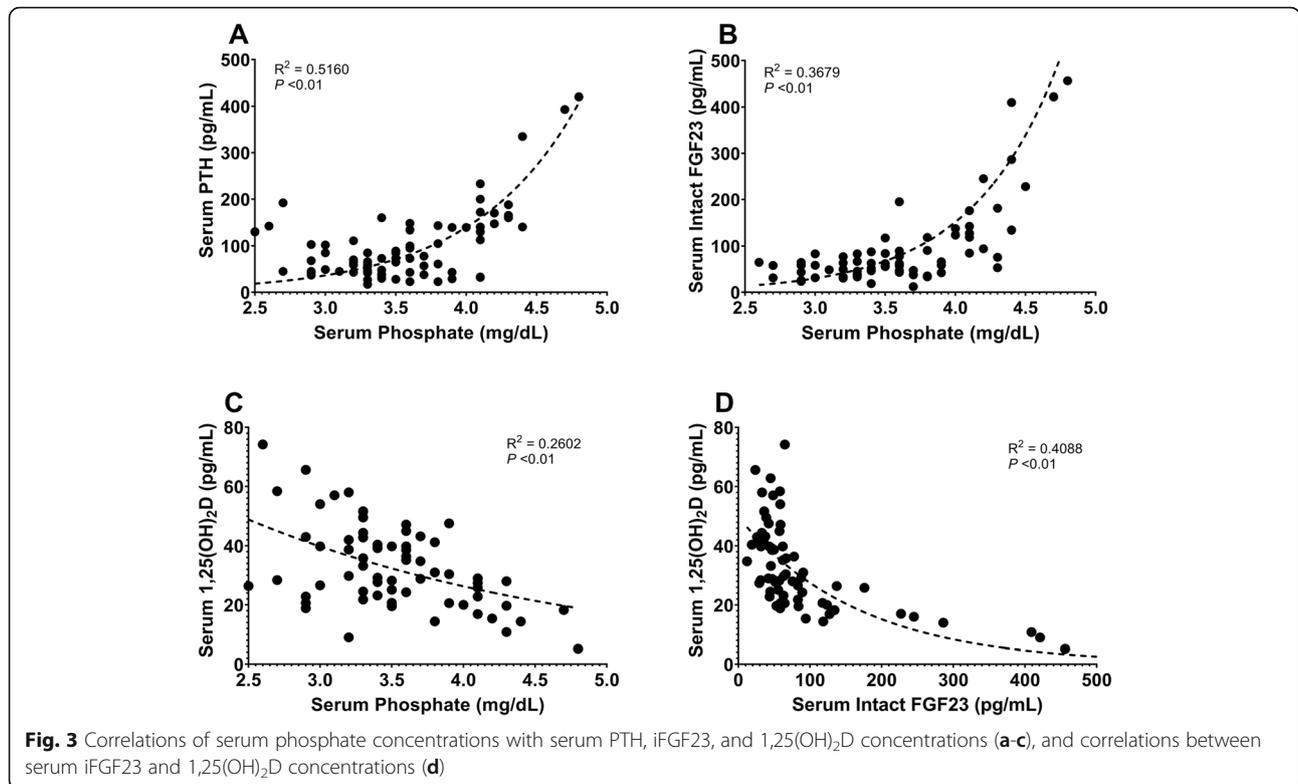


activity of FGF7 both *in vitro* and *in vivo*. A previous study demonstrated that FGF7 is overexpressed in some patients with mesenchymal tumors associated with osteomalacia, renal phosphate wasting, and hypophosphatemia.[6] The investigators found that FGF7 in tumor cell cultures inhibited *in vitro* sodium-dependent phosphate transport in opossum kidney proximal tubule cells, and that this inhibitory activity of tumor-derived cultures was abrogated by coinubation with neutralizing anti-FGF7 antibodies. Additionally, Bansal et al. described a patient with tumor-induced osteomalacia and

elevations in serum concentrations of both FGF7 and FGF23.[11] Interestingly, a recent study showed that low serum FGF7 concentrations were observed in pediatric patients with hypophosphatasia and hyperphosphatemia.[12] Moreover, the intravenous FGF7 administration increased the fractional excretion of phosphate *in vivo* in rats, suggesting that hyperphosphatemia in pediatric hypophosphatasia might be partly attributable to FGF7 insufficiency.

To our knowledge, the circulating concentration of the phosphatonin FGF7 in patients with CKD has not been





previously examined, and it is unknown whether FGF7 increases urinary phosphate excretion and facilitates normalization of serum phosphate concentration in early CKD. Our study failed to find evidence for compensatory increases in serum concentrations of FGF7 across CKD stages, suggesting that FGF7 may not play an important role in the pathophysiology of CKD-MBD in non-dialysis patients. Although a renal clearance study in human demonstrated the single-pass renal extraction of FGF23 (17.1%±19.5%) and PTH (44.2%±10.3%),[21] the data on renal FGF7 clearance are lacking. We postulate that FGF7 clearance may not be affected by kidney function. Furthermore, some uremic toxins may suppress phosphate-induced FGF7 production in patients with advanced CKD, thereby blunting compensatory increases in serum FGF7 concentrations. Alternatively,

phosphate-sensing receptor might be absent in FGF7-producing cells. Further studies are needed to determine which one of proposed possibilities contributes to a lack of change in serum FGF7 concentrations in CKD. This study has shown that circulating iFGF7 concentration was independently associated with increased BMI. The adipose tissue may contribute to the generation of FGF7 or, alternatively, FGF7 could affect adipocyte metabolism. The exact mechanism underlying the correlation between serum FGF7 concentration and body fat mass needs further study.

Consistent with previous studies, we found that low serum concentrations of 1,25(OH)₂D occur earlier in the course of the eGFR decline than do elevations in serum PTH concentrations.[22, 23] A reduction in renal mass, and accumulation of various factors such as FGF23,[24–

Table 2 Factors associated with highest intact FGF7 quartile by multivariate analysis

Variables	Adjusted Odds Ratio	P Value	95 % Confidence Interval
Male sex	0.47	0.22	0.14–1.56
Age (per 5 year increase)	0.86	0.13	0.73–1.07
Body mass index (per 5 kg/m ² increase)	1.20	0.01	1.12–1.55
Estimated GFR (per 5 mL/min/1.73 m ² increase)	0.89	0.06	0.79–1.09
Serum phosphate (per 1 mg/dL increase)	0.36	0.06	0.17–1.04
Serum 1,25(OH) ₂ D (per 1 pg/mL increase)	1.03	0.23	0.98–1.06

Quartile cutpoints for serum intact FGF7 concentration: 39.4, 46.4, 56.7 pg/mL

26] phosphate,[27, 28] PTH fragments,[29] and unmeasured uremic toxins could suppress the activity of renal 1-alpha-hydroxylase, thereby contributing to a reduction in serum 1,25(OH)₂D concentrations. Our results did not show significant relationships of serum 25(OH)D and 1,25(OH)₂D concentrations or kidney function, which are consistent with previous reports.[22, 25, 30, 31] These findings imply that the activity of renal 1-alpha-hydroxylase, rather than the abundance of circulating 25(OH)D, is the primary determinant of serum 1,25(OH)₂D concentration. Low serum concentrations of 1,25(OH)₂D augment PTH secretion by indirect and direct mechanisms. Indirect effects on PTH secretion occur through diminished intestinal absorption of calcium resulting in hypocalcemia. In addition, low 1,25(OH)₂D concentrations reduce the expression of the vitamin D receptor in parathyroid glands[32] and result in lower 1,25(OH)₂D-mediated suppression of PTH secretion.[33] Notably, the low prevalence of hyperphosphatemia in our cohort might be responsible for the lower PTH increase noted at reduced eGFR level in comparison to previous studies.[5, 34] The inter-assay variability in PTH measurements could also account for the difference in the eGFR cutpoint at which serum PTH concentrations increase.[35] This study confirms previous findings that a compensatory increase in circulating FGF23 concentrations commences before the occurrence of hyperphosphatemia.[5, 25] Nevertheless, in previous studies in which FGF23 increases occurred at relatively high eGFR levels, serum FGF23 concentration was measured using a C-terminal FGF23 immunoassay, which recognizes both iFGF23 and C-terminal FGF23 fragments.[5, 25, 36] We speculate that these findings are due to the impaired clearance of C-terminal FGF23 fragment relative to the clearance of iFGF23 in patients with CKD.[37–39].

The main strength of the current study is the comprehensive measurement of mineral metabolism biomarkers, including full-length biologically active forms of FGF7 and FGF23 as well as 1,25(OH)₂D, among patients with varying levels of eGFR. Our study also has some limitations. The biochemical data on other circulating phosphatonins, including matrix extracellular phosphoglycoprotein and secreted frizzled-related protein 4 (sFRP4), are lacking. Nonetheless, in a small study of patients with CKD, serum sFRP4 concentrations did not significantly change with creatinine clearance or serum phosphate concentrations.[40] In addition, our cohort comprised only non-dialysis patients; thus, these data may not be generalizable to patients receiving dialysis or to kidney transplant recipients. Moreover, cross-sectional analyses cannot determine causality.

Conclusions

The normalization of serum phosphate concentrations in early stages of CKD may be mainly mediated by compensatory decreases in circulating concentrations of 1,25(OH)₂D and increases in circulating concentrations of iFGF23 and PTH, while the phosphatonin iFGF7 may not play a crucial role in the compensatory response to phosphate retention in CKD-MBD. The longitudinal changes of mineral metabolism biomarkers and other circulating phosphatonins during the course of CKD need to be further explored.

Abbreviations

1,25(OH)₂D: 1,25-hydroxyvitamin D; 25(OH)D: 25-hydroxyvitamin D; BMI: Body mass index; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; FGF: Fibroblast growth factor; MBD: Mineral and bone disorder; PTH: Parathyroid hormone; sFRP4: Secreted frizzled-related protein 4

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Authors' contributions

K.K., J.M.H., R.J.S. and R.K. were involved in the research idea and study design. L.L., T.E.B., S.L.A. and J.M.H. were involved in data acquisition. K.K., T.E.B., S.L.A. and R.K. were involved in data analysis and interpretation. K.K. and R.K. were involved in statistical analysis and manuscript writing. A.A.S., R.J.S. and R.K. were involved in supervision and mentorship. All authors contributed to the final approval of the manuscript.

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Availability of data and materials

The dataset generated and/or analyzed during the current study is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Mayo Clinic Institutional Review Board (IRB reference number 19-010395). The study was reviewed by the Mayo Clinic IRB Ethics Committee and is determined to be exempt from the requirement for the informed consent in accordance with applicable HIPAA regulations (45 CFR 46.116d, category 1). This study was performed in compliance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

¹Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic, 200 1st Street SW, MN 55905 Rochester, USA. ²Division of Nephrology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand. ³Clinical Immunoassay Laboratory, Mayo Clinic, MN, Rochester, USA. ⁴Department of Laboratory Medicine and Pathology, Mayo Clinic, MN, Rochester, USA. ⁵Immunochemical Core Laboratory, Mayo Clinic, MN, Rochester, USA. ⁶Department of Biochemistry and Molecular Biology, Mayo Clinic, MN, Rochester, USA.

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