Clinical Kidney Journal, 2016, vol. 9, no. 5, 677–681

doi: 10.1093/ckj/sfw086
Advance Access Publication Date: 9 September 2016
Exceptional Case

EXCEPTIONAL CASE

Serum FGF23 levels may not be associated with serum phosphate and 1,25-dihydroxyvitamin D levels in patients with Fanconi syndrome–induced hypophosphatemia

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Abstract

Fibroblast growth factor 23 (FGF23) is regulated by sustained phosphate supplementation and restriction. However, few studies have investigated FGF23 levels in patients with Fanconi syndrome. Therefore, we evaluated intact and C-terminal FGF23 and FGF23-associated parameters in four patients with Fanconi syndrome. Serum intact and C-terminal FGF23 levels were extremely low. Although serum phosphate and 1,25-dihydroxyvitamin D levels improved to or above the normal range within 1 year of treatment with oral phosphate and calcitriol, serum FGF23 levels remained low. Serum FGF23 levels in patients with Fanconi syndrome might be regulated by novel factors other than serum phosphate and 1,25-dihydroxyvitamin D levels.

Key words: CKD, FGF-23, vitamin D

Background

Fibroblast growth factor 23 (FGF23) is a phosphaturic hormone produced by osteocytes and osteoblasts, and high serum FGF23 levels are a significant risk factor for patients with chronic kidney disease (CKD) [1, 2]. Serum FGF23 levels are regulated by several factors, among which phosphate is considered to be one of the primary regulators. However, the underlying mechanism by which phosphate regulates serum FGF23 levels remains unclear. For example, sustained dietary phosphate intake or restriction over several days changes serum FGF23 levels [3–5]. In contrast, another study demonstrated that one-time ingestion of phosphate does not increase serum FGF23 levels over a period of several hours [6].

Fanconi syndrome is a disorder characterized by functional defects of the proximal renal tubules, structures that absorb and secrete several substances, including phosphate. Patients with Fanconi syndrome exhibit low serum phosphate levels due to urinary excretion of phosphate. Serum phosphate levels in these patients remain low despite dietary or intravenous phosphate supplementation. However, to the best of our knowledge, few reports have described serum FGF23 levels in patients with Fanconi syndrome. Here, we examined serum

Received: April 26, 2016. **Accepted:** June 23, 2016

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FGF23 levels in patients with Fanconi syndrome–induced hypophosphatemia.

Case reports

We evaluated four patients with Fanconi syndrome–induced hypophosphatemia. Patient characteristics are shown in Table 1. All patients had moderate kidney dysfunction, hypophosphatemia, a low ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) and one or more of the following symptoms: glycosuria, metabolic acidosis, elevated urinary β2-microglobulin excretion levels and hyperuricosuria. Patients 1 and 2 were diagnosed upon renal biopsy and patients 3 and 4 were diagnosed by clinical findings. None of the patients had diabetes. Fanconi syndrome in all four patients was presumed to be the result of tubular damage caused by inflammation or nephrotoxic substances (Table 1).

None of the patients received oral phosphate at baseline. Calcitriol (0.75 μg) was administered to patient 2, but vitamin D analogues were not administered to the other three patients. Adefovir dipivoxil was administered to patients 3 and 4. After starting treatment, oral phosphate was administered to all patients, and patients 1 and 2 were also administered to calcitriol (Table 2). In addition, patient 1 was treated with prednisone. The dose of adefovir dipivoxil in patients 3 and 4 was tapered from 10 mg once daily to 10 mg every other day.

Changes in serum intact FGF23 and C-terminal FGF23 levels are shown in Figure 1. Intact FGF23 levels were measured using a chemiluminescence immunoassay (Kyowa Medex, Shizuoka, Japan) and C-terminal FGF23 levels were measured using a C-terminal FGF23 ELISA kit (Biomedica Immunoassays, Vienna, Austria). The normal ranges of these assays were defined according to previous reports or the manufacturer's data [7–10]. At baseline, serum intact FGF23 and C-terminal FGF23 levels were very low, and in three cases they were below the lower limit of detection. Three months after starting treatment, serum intact FGF23 (with the exception of patient 3) and C-terminal FGF23 levels remained below the normal range, although serum phosphate and 1,25-dihydroxyvitamin D levels were within or above the normal range. One year after starting treatment, serum intact FGF23 levels in patient 2 and C-terminal FGF23 in patients 2 and 3 remained below the normal range. Additionally, we measured serum intact FGF23 levels at each time point using a human intact FGF23 ELISA kit (Kainos Laboratories, Tokyo, Japan), an assay that is commonly used to measure intact FGF23. The results of this assay demonstrated that intact FGF23 levels in all patients were below the lower limit of detection at baseline and 3 months after starting treatment. In patients 1, 2 and 4, FGF23 levels remained below the lower limit of detection 1 year after starting treatment.

Changes in other parameters associated with CKD–mineral and bone disorder are shown in Figure 2. Phosphate and 1,25-dihydroxyvitamin D levels increased to normal or above-normal levels. TmP/GFR and estimated GFR increased in patients 1, 3 and 4, but did not change in patient 2, as the patient refused treatment for Fanconi syndrome. Alkaline phosphatase (ALP) levels decreased in all cases, but were still above the normal range after 1 year. Serum calcium levels did not change during the follow-up period, despite the administration of the appropriate therapy for 1 year.

Discussion

The present case series demonstrated that serum FGF23 levels were low in patients with Fanconi syndrome–induced hypophosphatemia and that serum FGF23 levels remained low despite the normalization of serum phosphate and 1,25-dihydroxyvitamin D levels. Although FGF23 levels in some patients normalized after the administration of oral phosphate and calcitriol, they were still near the lower limit of normal. All of the patients had stage 3 CKD, a stage at which serum FGF23 levels have typically already increased [11]. In a previous study we measured serum intact FGF23 levels in patients with CKD stages 1 and 2 [12]. The median of serum intact FGF23 levels in that study was 52.8 (interquartile range 36.0–74.9) pg/mL, which is much higher compared with the patients in this study. Therefore, we presume that serum FGF23 levels in the patients in this study are lower than in patients at the same stage of CKD.

Studies investigating FGF23 levels in patients with Fanconi syndrome are limited. To the best of our knowledge, this is the first study to investigate changes in serum FGF23 levels in patients with Fanconi syndrome–induced hypophosphatemia following the therapeutic normalization of serum phosphate and 1,25-dihydroxyvitamin D levels. Endo *et al.* [8] investigated serum intact FGF23 levels in patients with tumour-induced osteomalacia and X-linked hypophosphataemic rickets/

Table 1. Clinical and biochemical characteristics of the patients

	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	57	67	46	56
Sex	Female	Female	Male	Male
Cause of Fanconi syndrome	Tubulointerstitial nephritis	Proximal light chain tubulopathy	Adefovir	Adefovir
Creatinine (mg/dL)	1.87	1.27	1.49	1.3
eGFR (mL/min/1.73 m^2)	22.7	33.0	41.8	45.9
Albumin (g/dL)	4.1	4.4	4.8	4.6
Calcium (mg/dL)	9.2	9.6	9.7	9.2
Phosphate (mg/dL)	2.0	1.5	2.1	2.1
TmP/GFR (mg/dL)	0.7	0.5	0.8	1.2
Uric acid (mg/dL)	2.0	1.2	2.4	3.4
Fractional excretion of uric acid (%)	66	64	36	26
Bicarbonate (mmol/L)	20.4	18.6	23.6	23.7
Urine glucose	Yes	Yes	Yes	Yes
Urinary β2MG/Cr (mg/g Cr)	224	160	4	61

eGFR, estimated glomerular filtration rate; TmP/GFR, maximum tubular reabsorption rate of phosphate to glomerular filtration rate; β2MG/Cr, urinary β2-microglobulin/creatinine.

Table 2. Dose of oral phosphate and calcitriol

	Patient 1			Patient 2			Patient 3			Patient 4		
	Baseline	3 months	1 year	Baseline	3 months	1 year	Baseline	3 months	1 year	Baseline	3 months	1 year
Oral phosphate (mg/day)	0	500	200	0	900	900	0	1200	1200	0	600	600
Calcitriol (μg/day)	0	0.75	0.5	0.75	0.75	1	0	0	0	0	0	0

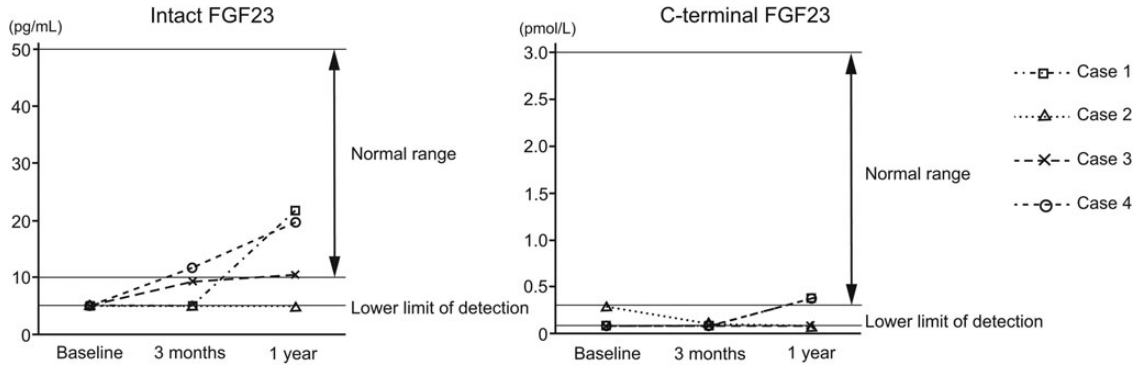

Fig. 1. Changes in serum intact FGF23 and C-terminal FGF23 levels.

osteomalacia as well as in patients with Fanconi syndrome. In that study, serum FGF23 levels in all patients with Fanconi syndrome–induced hypophosphatemia were <30 pg/mL and were undetectable (<3 pg/mL) in half of these patients. These results are consistent with the results of this study in that serum FGF23 levels at baseline were undetectable in most patients. In addition, case studies of three patients with adefovir- or tenofovir-induced Fanconi syndrome reported that the patients exhibited low serum FGF23 levels [13, 14]. However, other case studies have reported conflicting results with our findings [15–17]. Two patients with adefovir- or tenofovir-induced Fanconi syndrome exhibited elevated serum FGF23 levels at baseline and a reduction in FGF23 levels after the discontinuation of adefovir or tenofovir [15, 16]. In another case, serum FGF23 levels did not change following the discontinuation of tenofovir [17]. The mechanism by which adefovir- or tenofovir-induced Fanconi syndrome affected serum FGF23 levels in these patients is unclear. A previous cross-sectional study of patients without Fanconi syndrome demonstrated that serum FGF23 levels in patients taking tenofovir were comparable to patients not taking tenofovir [18], suggesting that tenofovir does not directly increase serum FGF23 levels. The discrepancies between these case studies might be due to comorbidities, concomitant medications, dietary phosphate load or the degree of tubular dysfunction. As with previous studies investigating serum FGF23 levels in patients with adefovir- or tenofovir-induced Fanconi syndrome, further studies are needed to elucidate the mechanism by which FGF23 levels are regulated in these patients.

Serum intact and C-terminal FGF23 levels in patients with Fanconi syndrome in this study were low, suggesting that decreases in FGF23 levels result from a decrease in FGF23 production rather than an increase in FGF23 degradation. However, the mechanism by which FGF23 production in patients with Fanconi syndrome decreases is unclear. Sustained phosphate and active vitamin D loading are the primary regulators of FGF23. However, serum FGF23 levels in this study were low despite the administration of oral phosphate and vitamin D analogues and normal serum phosphate and 1,25-dihydroxyvitamin D levels. Therefore, the regulation of FGF23 levels in patients with Fanconi syndrome might be associated with mechanisms independent of serum phosphate and 1,25-dihydroxyvitamin D levels. A previous study demonstrated that serum FGF23 levels in renal type IIa sodium/phosphate cotransporter knockout mice were lower than those in wild-type mice with similar serum phosphate levels [19]. These findings suggest that inhibiting phosphate reabsorption in the renal proximal tubules might decrease serum FGF23 levels via a novel mechanism that is independent of serum phosphate levels.

Oral phosphate loading regulates FGF23 levels under some conditions [3–5]. Therefore, despite the observation that serum phosphate levels improved to within normal range, the oral phosphate load administered to the patients in this study might not have been sufficient to stimulate FGF23 production, as phosphate is readily excreted in patients with Fanconi syndrome. In the aforementioned murine study, a high-phosphate diet increased serum FGF23 levels in renal type IIa sodium/phosphate cotransporter knockout mice [13], suggesting that excessive phosphate loading increases serum FGF23 levels in patients with Fanconi syndrome to the same extent it does in patients at the same stage of CKD. However, the mechanism by which bones sense the ingested phosphate levels is unclear. As serum phosphate levels improved to within the normal range, other factors might regulate the production of FGF23 in bones. We speculate that cells in the renal proximal tubules might sense the renal phosphorus absorption levels and influence the production of FGF23 accordingly. As the renal absorption of phosphorus was disrupted in patients with Fanconi syndrome, the renal proximal tubular cells might emit signals that inhibit the production of FGF23. However, the mechanism by which renal proximal tubular cells might relay signals to bone tissue is unclear and requires further investigation.

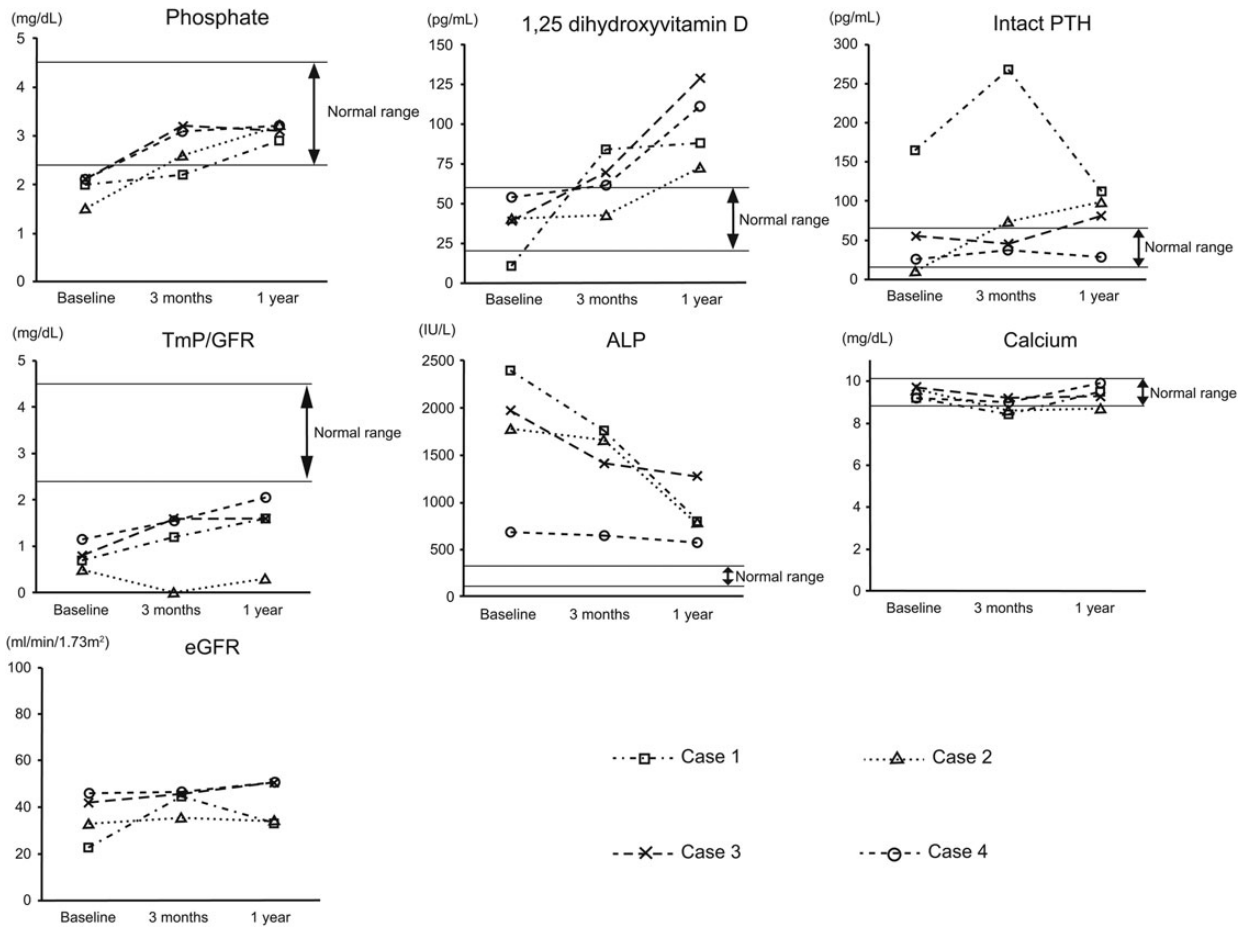

Fig. 2. Changes in parameters associated with CKD–mineral and bone disorder.

FGF23 is primarily produced in bones, indicating that bone diseases might lead to a reduction in FGF23 production. The patients in this study potentially had a bone disease, such as osteomalacia, as their serum ALP levels were elevated in the absence of liver disease. Serum FGF23 in patients with osteomalacia can vary depending on disease aetiology. In a small clinical study, children with rickets-like bone deformities had higher concentrations of plasma FGF23 compared with healthy controls, despite being calcium deficient [20]. In addition, a case study of a single patient with osteomalacia, resulting from familial intrahepatic cholestasis that was caused by defects in biliary epithelial transporters, reported that serum FGF23 levels were 10-fold higher compared with patients at the same stage of CKD [21]. These findings appear inconsistent with the hypothesis that osteomalacia might directly inhibit the production of FGF23 in bone tissue. Further studies are needed to determine if Fanconi syndrome–induced osteomalacia leads to a reduction in serum FGF23 levels.

Previous reports demonstrated that parathyroid hormone (PTH) stimulates the production of FGF23 [22, 23]. Therefore, PTH might be associated with serum FGF23 levels in patients with Fanconi syndrome. However, few of the patients in the present study exhibited elevated serum FGF23 and PTH levels, suggesting that serum FGF23 levels in patients with Fanconi syndrome are not associated with serum PTH levels.

In conclusion, patients with Fanconi syndrome–induced hypophosphatemia exhibited a reduction in serum FGF23 levels, despite the normalization of serum phosphate and 1,25-dihydroxyvitamin D levels. Therefore, serum FGF23 levels in patients with Fanconi syndrome might be regulated by novel factors rather than by serum phosphate and 1,25-dihydroxyvitamin D levels.

Conflict of interest statement

None declared.

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