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Administration of Ferric Citrate Hydrate Decreases Circulating FGF23 Levels Independently of Serum Phosphate Levels in Hemodialysis Patients with Iron Deficiency

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Key Words

Fibroblast growth factor 23 · Ferric citrate hydrate · Sevelamer-HCl · Parathyroid hormone · 1,25(OH)$_2$ vitamin D · Ferritin

Abstract

Background/Aim: Dietary phosphate intake and vitamin D receptor activator (VDRA) regulate fibroblast growth factor 23 (FGF23); iron may modulate FGF23 metabolism. We aimed to determine whether oral iron supplementation influences serum FGF23 concentration in hemodialysis (HD) patients, while excluding the effect of dietary phosphate intake. ***Methods:*** This prospective study enrolled 27 maintenance HD patients with iron deficiency and hyperphosphatemia treated with sevelamer-HCl. The phosphate binder was changed from sevelamer-HCl to ferric citrate hydrate (FCH) to maintain constant phosphate levels. VDRA, other phosphate binders, and cinacalcet HCl were not changed. Serum intact FGF23, C-terminal FGF23 (C-term FGF23), intact parathyroid hormone (PTH), 1,25(OH)$_2$D and other parameters were monitored for 12 weeks. ***Results:*** Serum phosphate levels (5.89 ± 1.45 mg/dl at baseline, 5.54 ± 1.35 mg/dl at 12 weeks) and 1,25(OH)$_2$D levels were unchanged. Serum ferritin levels increased from 25.6 ± 24.3 ng/ml at baseline to 55.8 ± 33.5 ng/ml at 12 weeks with FCH administration. Serum intact FGF23 and C-term FGF23 levels significantly decreased at 12 weeks compared with baseline (2,000 (1,300.0–3,471.4) to 1,771.4 (1,142.9–2,342.9) pg/ml, $p = 0.01$, and 1,608.7 (634.8–2,308.7) to 1,165.2 (626.1–1,547.8) RU/ml, $p = 0.007$, respectively); serum intact PTH levels significantly increased (96 (65–125) to 173 (114–283) pg/ml, $p < 0.001$). ***Conclusions:*** Oral FCH administration decreased serum intact FGF23 and C-term FGF23 levels and increased intact PTH levels; phosphate and 1,25(OH)$_2$D levels were unchanged. Oral FCH administration to treat iron deficiency is a possible strategy for reducing serum FGF23 levels independent of phosphate and VDRA.

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Background

Fibroblast growth factor 23 (FGF23) is a bone-derived hormone that plays an important role in systemic mineral handling. Serum FGF23 levels are elevated in chronic kidney disease (CKD) patients [1–5], and in-

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creased FGF23 levels are associated with a poor prognosis and increased cardiovascular events in these patients [6–9].

FGF23 secretion from osteoblastic cells is regulated by dietary phosphate intake [10], vitamin D receptor activator (VDRA) [11, 12], serum calcium levels [13], and parathyroid hormone (PTH) levels [14]. In addition to these regulating factors, iron has gained increased attention as a possible third factor regulating FGF23 [15]. Recent data from an animal study suggests that iron deficiency stimulates FGF23 transcription in osteocytes [16]. In humans, FGF23 levels are measured by using a C-terminal immunoassay (C-term FGF23). This assay detects both full-length FGF23 and its C-terminal fragments, which are inversely correlated with iron status [17, 18]. The level of full-length FGF23 assessed by the intact FGF23 immunoassay (intact FGF23), which measures biologically active FGF23, did not show a correlation with iron status [19]. On the other hand, in autosomal dominant hypophosphatemic rickets, which is characterized by impaired cleavage of intact FGF23, both C-term and intact FGF23 are inversely correlated with iron status [17]. Otherwise, although iron deficiency has been shown to increase FGF23 transcription, intact FGF23 levels do not increase in healthy humans under conditions of iron deficiency, possibly because they have normal FGF23 cleavage function. Moreover, an in vitro study in an osteoblastic cell line demonstrated that iron chelation with deferoxamine increases FGF23 mRNA expression by 20-fold in association with stabilization of hypoxia inducible factor-1α [16]. Taken together, these results suggest that iron deficiency stimulates FGF23 transcription.

Recent studies revealed that the administration of ferric citrate hydrate (FCH) reduces intact FGF23 levels in pre-dialysis CKD patients [19, 20]. FCH administration increased serum iron parameters and decreased phosphate levels [19, 20]. Because treatment with oral phosphate binders other than FCH also decreases serum FGF23 levels in CKD patients with hyperphosphatemia, presumably by inhibiting intestinal phosphate absorption [21], it is not clear whether oral iron supplementation influenced serum FGF23 levels in those trials [19, 20].

The aim of the current prospective clinical trial was to elucidate the effects of oral iron supplementation on serum FGF23 levels in CKD patients with iron deficiency. Although FGF23 is a key player in CKD mineral and bone disorder and influences mortality in CKD patients, the regulation of FGF23 has not been fully clarified. Elucidating whether oral iron supplementation influences FGF23 transcription and degradation is important in order to understand the regulation of FGF23. This is the first study to evaluate the influence of oral iron on serum FGF23 in hemodialysis (HD) patients.

Methods

Study Population and Design

We enrolled 28 patients at Ojiya General Hospital. The patients were 20 years of age or older and had been maintained for at least 1 year with HD treatment (3 sessions per week of >4 h). All patients were treated with standard HD mode. The dialysate calcium ion concentration was 3.0 mEq/l, and this value did not change over the 12-week period. The inclusion criteria were as follows: (1) hyperphosphatemia (iP >6.0 mg/dl if patients were not treated with phosphate binders) that was treated with sevelamer-HCl and (2) iron deficiency, defined as a serum ferritin level <100 ng/ml or serum ferritin level 100–300 ng/ml and transferring saturation (TSAT) <20% [21]. The exclusion criteria were as follows: (1) patients with cancer, hematological disease or an active infection and (2) patients whose serum phosphate level was <3.5 mg/dl.

The study protocol was performed in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the human research committee at our institution (authorization No. 1401). Written informed consent was obtained from all participants. The study is registered with the UMIN Clinical Trials Registry (No. 000013972).

This study was a prospective, open-label interventional study. Patients who were treated with intravenous saccharated ferric oxide were required to discontinue treatment 4 weeks prior to commencement of the study. At trial initiation, the phosphate binder was changed from sevelamer-HCl to FCH (Torii Pharmaceutical, Co., Ltd., Tokyo, Japan) for all patients. The conversion rate from sevelamer-HCl to FCH was set at 1:0.45 to maintain the phosphate level. The dosages of VDRA, other phosphate binders, cinacalcet HCl and dialysate were not changed during the study period.

Laboratory Testing

Blood samples were obtained at the start of the dialysis session for baseline measurements and at weeks 3 and 12. Serum phosphorus, calcium, magnesium, alkaline phosphatase, iron, TSAT, ferritin, hemoglobin and C-reactive protein were measured by using standard methods. Serum calcium levels were corrected for albumin concentration by using the Payne's formula. Serum intact PTH levels were measured by using a second-generation PTH assay (Architect; Abbott Japan Co., Ltd., Tokyo, Japan). Serum intact FGF23 and C-term FGF23 levels were determined by using a sandwich ELISA kit (Immutopics International, San Clemente, Calif., USA). Serum 1,25(OH)$_2$D was measured by using a radioimmunoassay (SRL, Tokyo, Japan).

Statistical Analysis

Intact FGF23, C-term FGF23 and intact PTH are expressed as the median (interquartile range); all other parameters are expressed as the mean ± SD. The data in each time point were compared by using the Wilcoxon signed-rank test. Because serum intact FGF23 and C-term FGF23 were not normally distributed,

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we analyzed log-transformed values in the analyses. Statistical analysis was performed by using JMP 11.0.0 (SAS Institute, Cary, N.C., USA). A p value of <0.05 was considered statistically significant.

Results

Clinical Characteristics

A total of 28 patients were enrolled in the study. One patient was withdrawn because of diarrhea caused by FCH; therefore, 27 patients were included in the final analysis. The patients' baseline characteristics are shown in table 1. The serum ferritin levels were lower than 100 ng/ml in 26 patients, and the TSAT was lower than 20% in 15 patients. All patients were diagnosed as iron deficient.

Effect of FCH on Iron-Related Factors and Anemia

Serum iron, TSAT and serum ferritin levels were significantly elevated over the study period (TSAT: 20.4 ± 8.4% at baseline, 32.4 ± 16.2% at 3 weeks, 33.5 ± 13.2% at 12 weeks; serum ferritin: 25.6 ± 24.3 ng/ml at baseline, 43.2 ± 21.7 ng/ml at 3 weeks, 55.8 ± 33.5 ng/ml at 12 weeks; fig. 1). At 12 weeks, 4 patients were no longer considered iron deficient, and 23 patients remained iron deficient. Although the darbepoetin dose was decreased, the hemoglobin levels became significantly elevated with improvement of iron deficiency (10.6 ± 1.0 g/dl at baseline, 11.3 ± 1.0 g/dl at 3 weeks and 12.3 ± 1.6 g/dl at 12 weeks).

Effect of FCH on CKD Mineral and Bone Disorder-Related Parameters

The phosphate levels remained stable (table 2). The intact FGF23 levels were 2,000 (1,300.0–3,471.4) pg/ml at baseline, and these levels decreased to 2,085.7 (1,442.9–3,228.6) pg/ml (p = 0.49) at 3 weeks and to 1,771.43 (1,142.9–2,342.9) pg/ml (p = 0.01) at 12 weeks (fig. 2). The C-term FGF23 levels were 1,608.7 (634.8–2,308.7) RU/ml at baseline, and these levels decreased to 1,495.6 (773.9–2,139.1) RU/ml (p = 0.79) at 3 weeks and to 1,165.2 (626.1–1,547.8) RU/ml (p = 0.007) at 12 weeks (fig. 3). The ratios of intact FGF23 to C-term FGF23 were 1.078 ± 0.088 at baseline, 1.072 ± 0.041 at week 3 and 1.080 ± 0.048 at week 12. No significant differences were found in these ratios (fig. 4). The intact PTH levels were 96 (65–125) pg/ml at baseline, with a significant increase to 173 (114–283) pg/ml at 12 weeks (p < 0.001; fig. 5). The 1,25(OH)$_2$D levels remained unchanged in both patients with and without active vitamin D (table 2).

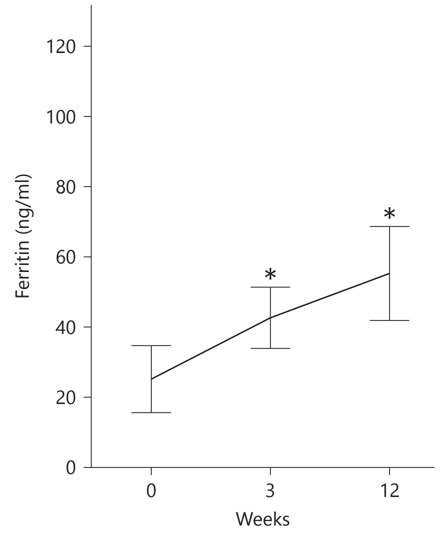

Fig. 1. Mean ferritin level after switching from sevelamer-HCl to FCH. The error bars represent the SD. * p < 0.001 compared with 0 weeks.

Table 1. Baseline characteristics of the study participants

Characteristic	All patients (n = 27)
Sex, M/F	18/9
Mean age, years	62.6±15.7
Cause of ESRD (DM/non-DM)	7/20
Dialysis duration, years	12.6±7.9
Dialysis time, h/session	4.28±0.38
Dialysate calcium ion, mEq/l	3.0
Use of darbepoetin, µg/week	24.7±21.0
Use of VDRA	
Intravenous calcitriol	13
Oral alfacalcidol	1
Non user	13
Use of cinacalcet HCl	13

ESRD = End-stage renal disease; DM = diabetes mellitus.

Discussion

This trial showed that, in HD patients, switching from sevelamer-HCl to FCH decreased both intact and C-term FGF23 levels, while intact PTH levels were elevated. The iron load would have been the main cause of altered circulating FGF23 levels due to FCH administration because the phosphate levels did not change.

Wolf et al. [22] compared the effects of intravenous iron in the form of ferric carboxymaltose (FCM) with iron dextran on serum FGF23 levels in women with iron-deficiency

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Table 2. Laboratory data during administration with FCH

	Baseline	Week 3	Week 12
Phosphorus, mg/dl	5.89±1.45	5.65±1.37	5.54±1.35
Calcium, mg/dl	9.40±0.57	9.46±0.60	9.37±0.87
Magnesium, mg/dl	2.96±0.51	2.97±0.53	2.93±0.57
1,25(OH)$_2$D, pg/ml			
User of VDRA (n = 14)	11.42±4.75	13.11±5.48	11.08±4.72
Non user (n = 13)	6.23±2.93	7.37±3.86	7.11±2.48
Intact PTH, pg/ml	114.0±101.6	139.3±107.0**	206.4±130.4**
Iron, µg/dl	58.7±22.9	87.6±49.4*	77.6±28.9*
TSAT, %	20.4±8.4	32.4±16.2*	33.5±13.2**
Ferritin, ng/ml	25.6±24.3	43.2±21.7**	55.8±33.5**
Hemoglobin, g/dl	10.6±1.0	11.3±1.0**	12.3±1.6**
ALP, U/l	249.2±86.0	244.6±82.4	244.5±83.2
CRP, mg/dl	0.26±0.42	0.39±0.88	0.36±0.55
BUN, mg/dl	60.1±14.5	59.1±9.9	58.4±11.3
Cr, mg/dl	11.9±2.5	12.4±2.6	12.1±2.8
Kt/V	1.33±0.17	1.32±0.17	1.33±0.19
FCH, mg/day	1,175.9±595.7	1,148.1±560.1	1,148.1±560.1
Darbepoetin, µg/week	24.7±21.0	24.7±21.0	21.0±18.1

* $p < 0.05$, ** $p < 0.001$, as compared with baseline.

ALP = Alkaline phosphatase; BUN = blood urea nitrogen; CRP = C-reactive protein; Kt/V = single-pool Kt/V.

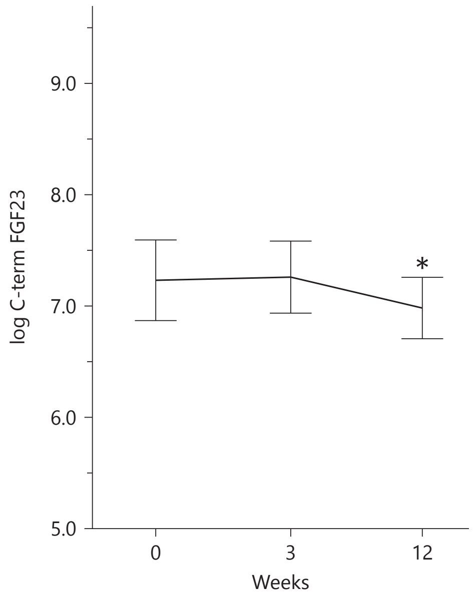

Fig. 3. Median log of C-term FGF23 after switching from sevelamer-HCl to FCH. The error bars represent the interquartile range. * p = 0.007 compared with 0 weeks.

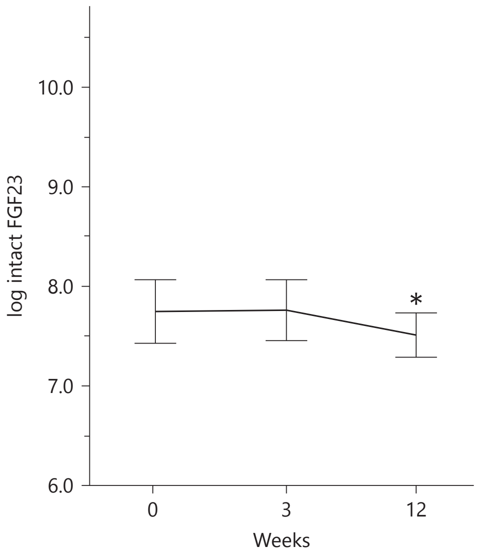

Fig. 2. Median log of intact FGF23 after switching from sevelamer-HCl to FCH. The error bars represent the interquartile range. * p = 0.01 compared with 0 weeks.

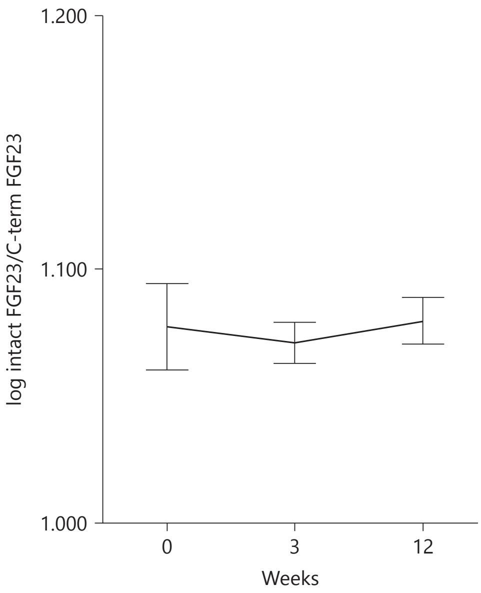

Fig. 4. Mean log of intact FGF23/log of C-term FGF23 after switching from sevelamer-HCl to FCH. The error bars represent the SD.

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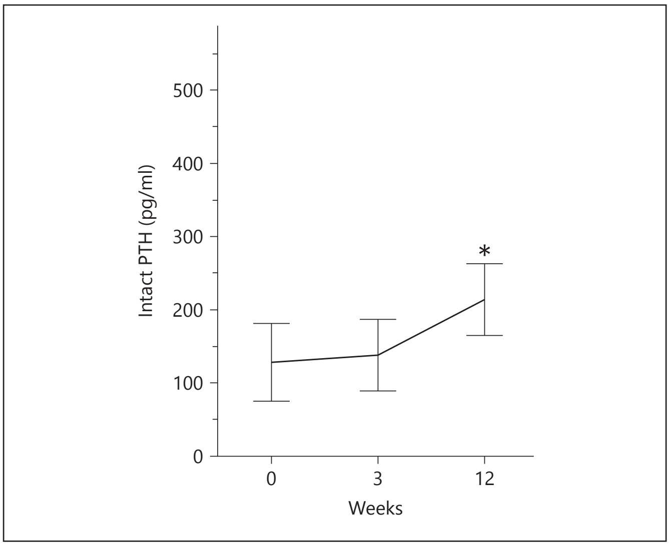

Fig. 5. Median intact PTH level after switching from sevelamer-HCl to FCH. The error bars represent the interquartile range. * $p < 0.001$ compared with 0 weeks.

anemia. Although both intravenous FCM and iron dextran decreased serum C-term FGF23 levels, FCM increased serum intact FGF23 levels and decreased serum phosphate levels despite no change in iron dextran. Thus, these authors hypothesized that FCM and iron dextran could reduce FGF23 transcription, but that the causative agents were the carbohydrate moieties of FCM rather than iron dextran, and the effect was due to inhibition of FGF23 degradation.

In the current study, switching to administration of FCH from sevelamer-HCl reduced intact FGF23 and C-term FGF23. The iron elements of FCH might suppress the transcription of FGF23 in osteocytes. Intact FGF23 represents full-length FGF23, and C-term FGF23 represents full-length FGF23 and the C-terminal fragment. Therefore, the ratio of intact to C-term FGF23 indicates the amount of degradation of full-length FGF23. The ratio of intact to C-term FGF23 did not change, suggesting that oral intake of FCH has less influence on FGF23 degradation. A recent study, which evaluated the chronic effect of iron supplementation, showed that the role of iron on the degradation of circulating intact FGF23 might differ between the acute and the chronic phases of iron-deficiency anemia (David et al. [13] TH-OR102, ASN2014). This finding may help to explain why the suppression of FGF23 production had a greater impact than the suppression of FGF23 degradation in our HD patients with iron deficiency.

Reduction of FGF23 resulted in elevation of intact PTH levels in the current study. The relationship between FGF23 and PTH is controversial. FGF23 suppresses the synthesis of PTH through its direct action on the parathyroid glands [23, 24]. However, the relationship between FGF23 and PTH is not fully understood, as the regulation of FGF23 and PTH is complex, and indirect relationships via VDRA and/or phosphate balance exist. In the current study, the decreased direct suppression effect of FGF23 on the parathyroid glands may have caused PTH elevation because the serum phosphate, calcium and $1,25(OH)_2D$ levels were constant. Oral treatment with FCH modestly increased serum intact PTH levels in HD patients, although it reduced phosphate levels [25]. It is possible that reduction of FGF23, which is caused by oral treatment with FCH, directly influences elevation of PTH levels. Takeda et al. [26] reported that serum PTH levels decrease with elevation of FGF23 in HD patients. These previous studies suggest that FGF23 and PTH form a negative endocrine feedback loop.

Although PTH has been recognized as a uremic toxin since the 1970s [27], modern clinical studies have reported surprisingly limited impact of elevated PTH levels on mortality in CKD patients [28–30]. Other studies demonstrated that increased FGF23 predicted mortality and cardiovascular events in CKD patients [8, 9]. If circulating FGF23 and PTH levels generally run counter to each other, the harm of elevated PTH levels might be offset by decreased FGF23 levels. Therefore, data from future studies investigating the mortality risk of PTH levels in CKD patients should be considered with regard to FGF23 levels.

This study has some limitations. First, no control patients were used; thus, a crossover study will be required to confirm the results. Second, as this was a small open-label trial of short duration, conclusions about the long-term efficacy cannot be extrapolated. Further studies are required for confirming whether iron supplementation per se is capable to reduce the circulating FGF23 levels.

In conclusion, in HD patients with iron deficiency, switching the phosphate binder from sevelamer-HCl to FCH decreased serum FGF23 levels and increased serum PTH levels, despite the fact that the phosphate levels remained unchanged. Oral iron administration possibly reduces serum FGF23 levels independently of phosphate and VDRA. The reduction of FGF23 caused by FCH directly increased serum PTH levels.

Disclosure Statement

J.J.K. and I.N. received lecturer fee from Torii Pharmaceutical Co., Ltd.

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