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ORIGINAL ARTICLE

Effect of ferric citrate hydrate on FGF23 and PTH levels in patients with non-dialysis-dependent chronic kidney disease with normophosphatemia and iron deficiency

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Abstract

Background In patients with normophosphatemia with chronic kidney disease (CKD), fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH) increase urinary phosphate excretion while maintaining serum phosphate within the normal range. Recent reports have shown that, in this stage, phosphate binders do not decrease serum FGF23 and PTH levels. Iron deficiency promotes transcription of FGF23 and iron-supplementation for iron deficiency decreases serum FGF23 levels. We hypothesized that ferric citrate hydrate, an iron-based phosphate binder, will decrease serum FGF23 levels in patients with non-dialysis-dependent CKD with normophosphatemia and iron deficiency.

Methods This was a single-center, randomized, open-label interventional study. The inclusion criteria were as follows: (1) eGFR < 45 mL/min/1.73 m^2, (2) normophosphatemia, (3) iron deficiency. Patients were assigned to the following groups: ferric citrate hydrate (FCH)-group, sodium ferrous citrate (SFC)-group, and control-group. After 12 weeks of intervention, we evaluated serum FGF23 levels and CKD-mineral bone disorder markers.

Results There were 17 patients in the FCH-group, 14 in the SFC-group, and 9 in the control-group. The serum ferritin levels increased in the FCH-group and SFC-group compared with baseline. Serum FGF23 levels were unchanged; the change in the FCH-group was from 52.91 RU/mL (42.48–72.91) to 40.00 RU/mL (30.30–58.13) ($P = 0.1764$). However, in the FCH-group, serum PTH levels significantly decreased compared with baseline, from 68.00 pg/mL (49.00–141.00) to 60.00 pg/mL (44.00–144.00) ($P = 0.0101$).

Conclusion Iron-based phosphate binder did not decrease serum FGF23 levels, but decreased serum PTH levels.

Keywords FGF23 · PTH · Ferric citrate hydrate · Iron deficiency · Normophosphatemia

Introduction

Phosphate homeostasis in CKD

Hyperphosphatemia in patients with chronic kidney disease (CKD) is associated with poor prognosis, cardiovascular events, poor renal outcomes, vascular calcification, and atherosclerosis; therefore, phosphate restriction and treatment with phosphate binders are recommended in the stage of pre-dialysis with hyperphosphatemia [1, 2]. However, in patients with CKD, serum phosphate (iP) levels remain within the normal range until the end stage of renal disease. This is because of secretion of fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH), which promote urinary phosphate excretion as glomerular filtration rate (GFR) declines [3].

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Recent data have shown that increased FGF23 levels are associated with a poor prognosis because they result in increased adverse cardiovascular events and poor renal outcomes in these patients, and increased PTH levels are also associated with a poor prognosis [4–6].

In patients with CKD with hyperphosphatemia, phosphate binders decrease serum FGF23 and PTH levels along with serum phosphate levels [7–9].

In patients with CKD with normophosphatemia, phosphate homeostasis is maintained by increased levels of FGF23 and PTH despite declining GFR. Can phosphate binders decrease serum FGF23 or PTH levels in this stage? Although results of previous studies are conflicting, negative evidence is superior [10–17].

FGF23 and iron

FGF23 is regulated by oral phosphate intake, 1,25-dihydroxyvitamin D, PTH, and calcium. In addition to these factors, it was reported that intravenous administration of iron increased serum intact-FGF23 levels and decreased serum C-FGF23 levels [18–20]. The increased intact-FGF23 and decreased C-FGF23 indicate inhibition of degradation of FGF23. Moreover, because this effect was seen only with ferric carboxymaltose and saccharated ferric oxide, and not with iron dextran, it was thought that the degradation of FGF23 was inhibited by the additives and not by iron [20]. Furthermore, recent studies have showed that iron deficiency results in increased transcription of FGF23 [21, 22]. Moreover, iron supplementation decreased transcription of FGF23 [20].

FGF23 and ferric citrate hydrate

Ferric citrate hydrate (FCH), an iron-based phosphate binder, decreases serum FGF23 levels in patients with CKD [23, 24]. Although administration of FCH might decrease serum FGF23 levels by decreasing oral phosphate loading, administration of FCH also showed the effect of iron supplementation. This lowering of serum FGF23 levels is independent of serum phosphate levels, and iron supplementation results in decreased serum FGF23 levels [25].

We hypothesized that FCH will decrease serum FGF23 levels in patients with non-dialysis-dependent CKD with normophosphatemia with iron deficiency. This effect was not clearly established with other phosphate binders. We examined whether FCH reduced serum FGF23 levels in patients with non-dialysis-dependent CKD with normophosphatemia and iron deficiency, and assessed the phosphate binding and iron supplementation effects. We also administered sodium ferrous citrate (SFC) as pure iron supplementation in some participants to investigate the phosphate binding and iron supplementation effects on serum FGF23 levels.

Method

The study was designed as a single-center, randomized, open-label interventional study. We enrolled 50 patients at Saiseikai Niigata Daini Hospital. The patients were 20 years of age or older. The inclusion criteria were as follows: (1) eGFR < 45 mL/min/1.73 m^2, (2) normophosphatemia; serum phosphate level: 2.5–4.5 mg/dL (normal value at this institution) [2], (3) iron deficiency; serum ferritin level < 100 ng/mL, or serum ferritin level 100–300 ng/mL with transferring saturation (TSAT) < 20%. The exclusion criteria were as follows: (1) patients currently on other phosphate binders or iron supplementation, (2) patients with cancer, hematological diseases, or an active infection. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the human research committee at our institution (authorization No. E15-16). Written informed consent was obtained from all the participants. The study is registered with the UMIN Clinical Trials Registry (No. 000020935).

Participants were randomized into the following groups: FCH-group, SFC-group, and control-group. The outpatients on Fridays were assigned to the FCH-group while the outpatients on Tuesdays and Thursdays were assigned to the SFC-group and control-group, respectively. Two patients in the FCH-group and five patients in the SFC group were excluded because they refused to provide informed consents. The observational period was 12 weeks because FCH reduces serum FGF23 levels by 12 weeks [25]. The FCH-group was administered a tablet of FCH (250 mg) with each meal. The SFC-group received a tablet of SFC (50 mg) once a day. Iron content of FCH is 60 mg per tablet of 250 mg FCH. Therefore, the FCH-group received 180 mg iron per day. It was reported that the absorption rate of Fe^{2+} and Fe^{3+} is in the ratio of 5:1. Thus, the same amount of iron is absorbed with FCH 750 mg per day as with SFC 36 mg [26]. Therefore, we chose FCH 750 mg and SFC 50 mg to make meaningful comparisons.

Laboratory testing

Blood samples were obtained before initiating therapy for baseline measurements and at 12 weeks. Serum creatinine, phosphorus, calcium, magnesium, iron, TSAT, ferritin, hemoglobin, platelet count, and C-reactive protein were measured using standard methods. Serum calcium levels were corrected for albumin concentrations using Payne's formula. Serum intact PTH levels were measured using a second-generation PTH assay (Architect; Abbott Japan

Co., Ltd., Tokyo, Japan). Serum intact FGF23 and C-term FGF23 levels were determined using a sandwich ELISA kit (Immutopics International, San Clemente, CA, USA).

Statistical analysis

Intact FGF23, C-term FGF23, and intact PTH are expressed as median (interquartile range); all other parameters are expressed as mean ± SD. The data at each time point were compared using Wilcoxon signed-rank test. Statistical analysis was performed using JMP 11.0.0 (SAS Institute, Cary, NC, USA). A P value of < 0.05 was considered statistically significant.

Result

Clinical characteristics

One patient withdrew from the study because of diarrhea caused by FCH. Three patients were lost to follow-up in each of the three groups. Therefore, 40 patients were included in the final analysis with 17, 14, and 9 patients in the FCH-group, SFC-group, and control-group, respectively. The patients' baseline characteristics are shown in Table 1. The average eGFR of FCH-group and SFC-group at baseline was lower than that of the control-group, but the difference was not significant. The eGFR of FCH-group was 22.92 ± 11.38 mL/min/1.73 m^2 ($P = 0.1181$) and FSC-group was 26.09 ± 7.51 mL/min/1.73 m^2 ($P = 0.1227$) compared with the control-group 31.27 ± 10.09 mL/min/1.73 m^2.

CRP level in the FCH-group was significantly higher than in the control-group ($P = 0.0043$). Hemoglobin level in the FCH-group was significantly lower than in the control-group ($P = 0.0204$).

Effect of FCH and SFC

In the FCH-group, eGFR was noted to be significantly declined (22.92 ± 11.38 mL/min/1.73 m^2 at baseline, 22.16 ± 11.39 mL/min/1.73 m^2 at week 12, $P = 0.0454$) and in SFC-group, eGFR was significantly elevated compared with baseline (26.09 ± 7.51 mL/min/1.73 m^2 at baseline, 28.53 ± 10.97 mL/min/1.73 m^2 at week 12, $P = 0.0338$). In the FCH-group and SFC-group, serum ferritin levels were significantly elevated compared with baseline (in FCH-group 44.24 ± 24.36 ng/mL at baseline, 80.68 ± 33.97 ng/mL at week 12, $P < 0.0001$; in SFC-group 46.96 ± 27.67 ng/mL at baseline, 57.95 ± 30.50 ng/mL at week 12, $P = 0.0392$). Hemoglobin levels in each group were unchanged. In the SFC-group, platelet count significantly declined compared with baseline ($P = 0.0026$). In the three groups, serum iP levels were unchanged. Serum FGF23 levels did not significantly change compared with the baseline. In the FCH-group, C-FGF23 level was 52.91 RU/mL (42.48–72.91) at baseline, 40.00 RU/mL (30.30–58.13) at week 12 ($P = 0.1764$), and intact-FGF23 level was 37.64 pg/mL (21.93–56.21) at baseline and 34.79 pg/mL (20.50–70.50) at week 12 ($P = 0.4043$). In the SFC-group, C-FGF23 level was 34.65 RU/mL (29.87–50.52) at baseline and 33.35 RU/mL (30.96–52.04) at week 12 ($P = 0.2531$), and intact-FGF23 level was 24.79 pg/mL (9.07–44.79) at baseline

Table 1 Baseline characteristics of the participants

	Ferric citrate hydrate	Sodium ferrous citrate	Control	Significance	
n	17	14	9	FCH vs. control	SFC vs. control
Age (year)	74.76 ± 9.02	66.71 ± 9.31	66.44 ± 20.92	0.4663	0.5705
Gender (M/F)	6/11	7/7	2/7	0.4920	0.1828
Disease (DM/notDM)	4/13	6/8	1/8	0.4447	0.1063
eGFR (mL/min/1.73 m^2)	22.92 ± 11.38	26.09 ± 7.51	31.27 ± 10.09	0.1181	0.1227
iP (mg/dL)	3.59 ± 0.75	3.56 ± 0.55	3.59 ± 0.59	0.9784	0.9748
cCa (mg/dL)	9.08 ± 0.40	9.00 ± 0.32	9.22 ± 0.40	0.2023	0.0622
Mg (mg/dL)	2.30 ± 0.30	2.26 ± 0.18	2.12 ± 0.25	0.2302	0.3056
iPTH (pg/mL)	68.00 (49.00–141.00)	86.00 (62.25–117.75)	62.00 (46.00–83.00)	0.5001	0.3777
iFGF23 (pg/mL)	37.64 (21.93–56.21)	24.79 (9.07–44.79)	34.79 (29.07–49.07)	0.9785	0.2565
CFGF23 (RU/mL)	52.91 (42.48–72.91)	34.65 (29.87–50.52)	50.30 (36.39–65.96)	0.5176	0.1753
Fe (μg/dL)	77.18 ± 28.94	84.36 ± 24.32	88.11 ± 24.03	0.4034	1.0000
TSAT (%)	24.52 ± 9.74	29.16 ± 10.82	30.43 ± 7.05	0.1059	0.8255
Ferritin (ng/mL)	44.24 ± 24.36	46.96 ± 27.67	36.82 ± 14.40	0.6663	0.2984
CRP (mg/dL)	0.20 ± 0.2913	0.07 ± 0.08	0.02 ± 0.02	0.0043*	0.1328
Hb (g/dL)	11.27 ± 1.36	11.99 ± 1.90	12.58 ± 1.02	0.0204*	0.3442
Plt (10^4/μL)	19.22 ± 4.43	22.11 ± 5.53	22.58 ± 4.58	0.0556	0.6141

and 20.50 pg/mL (11.93–42.29) at week 12 ($P = 0.4263$). In the control-group, C-FGF23 level was 50.30 RU/mL (36.39–65.96) at baseline and 59.87 RU/mL (32.04–63.35) at week 12 ($P = 0.5898$), and intact-FGF23 level was 34.79 pg/mL (29.07–49.07) at baseline and 33.21 pg/mL (26.50–35.07) at week 12 ($P = 0.4259$). However, serum C-FGF23 level in the FCH-group was lower. In the FCH-group, serum intact-PTH level significantly decreased compared with baseline (68.00 pg/mL (49.00–141.00) at baseline, 60.00 pg/mL (44.00–144.00) at week 12, $P = 0.0101$), while in the SFC-group and control-group intact-PTH levels did not significantly change compared with baseline (SFC-group 86.00 pg/mL (62.25–117.75) at baseline and 79.50 pg/mL (50.00–140.75) at week 12 ($P = 0.4939$); control-group 62.00 pg/mL (46.00–83.00) at baseline and 71.00 pg/mL (57.00–129.00) at week 12, $P = 0.1250$) (Table 2; Fig. 1).

Table 2 Treatment effect

	Ferric citrate hydrate			Sodium ferrous citrate			Control		
	Baseline	Week 12	*P*	Baseline	Week 12	*P*	Baseline	Week 12	*P*
eGFR (mL/min/1.73 m2)	22.92 ± 11.38	22.16 ± 11.39	0.0454*	26.09 ± 7.51	28.53 ± 10.97	0.0338*	31.27 ± 10.09	32.06 ± 10.59	0.3672
iP (mg/dL)	3.59 ± 0.75	3.41 ± 0.87	0.1775	3.56 ± 0.55	3.36 ± 0.54	0.0838	3.59 ± 0.59	3.44 ± 0.52	0.2109
cCa (mg/dL)	9.08 ± 0.40	9.13 ± 0.39	0.3515	9.00 ± 0.32	8.92 ± 0.28	0.1230	9.22 ± 0.40	9.14 ± 0.39	0.2109
Mg (mg/dL)	2.30 ± 0.30	2.41 ± 0.57	0.2261	2.26 ± 0.18	2.17 ± 0.16	0.0708	2.12 ± 0.25	2.12 ± 0.24	0.3984
iPTH (pg/mL)	68.00 (49.00–141.00)	60.00 (44.00–144.00)	0.0101*	86.00 (62.25–117.75)	79.50 (50.00–140.75)	0.4939	62.00 (46.00–83.00)	71.00 (57.00–129.00)	0.1250
iFGF23 (pg/mL)	37.64 (21.93–56.21)	34.79 (20.50–70.50)	0.4043	24.79 (9.07–44.79)	20.50 (11.93–42.29)	0.4263	34.79 (29.07–49.07)	33.21 (26.50–35.07)	0.4259
CFGF23 (RU/mL)	52.91 (42.48–72.91)	40.00 (30.30–58.13)	0.1764	34.65 (29.87–50.52)	33.35 (30.96–52.04)	0.2531	50.30 (36.39–65.96)	59.87 (32.04–63.35)	0.5898
Fe (μg/dL)	77.18 ± 28.94	74.24 ± 28.43	0.4222	84.36 ± 24.32	81.71 ± 28.40	0.2762	88.11 ± 24.03	89.89 ± 24.20	0.5781
TSAT (%)	24.52 ± 9.74	25.01 ± 8.53	0.3687	29.16 ± 10.82	30.90 ± 11.68	0.1629	30.43 ± 7.05	29.59 ± 8.37	0.3262
Ferritin (ng/mL)	44.24 ± 24.36	80.68 ± 33.97	< 0.0001*	46.96 ± 27.67	57.95 ± 30.50	0.0392*	36.82 ± 14.40	34.92 ± 14.95	0.3262
CRP (mg/dL)	0.20 ± 0.2913	0.48 ± 0.80	0.1446	0.07 ± 0.08	0.08 ± 0.09	0.2158	0.02 ± 0.02	0.02 ± 0.01	0.3125
Hb (g/dL)	11.27 ± 1.36	11.93 ± 1.72	0.1080	11.99 ± 1.90	12.03 ± 1.43	0.7555	12.58 ± 1.02	12.44 ± 1.28	0.2441
Plt (104/μL)	19.22 ± 4.43	18.30 ± 4.56	0.1616	22.11 ± 5.53	20.36 ± 4.06	0.0026*	22.58 ± 4.58	22.04 ± 5.20	0.3535

*$P < 0.05$ compared with baseline

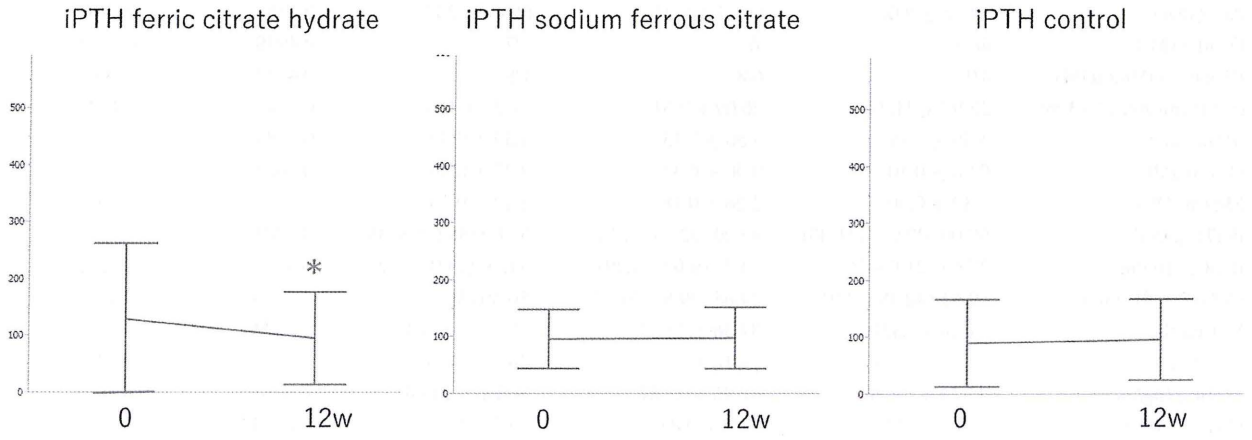

Fig. 1 Intact-PTH levels at baseline and week 12 in ferric citrate hydrate group, sodium ferrous citrate group, and control group. *$P < 0.05$ compared with baseline

Discussion

In this open-label interventional study, treatment with FCH in patients with non-dialysis-dependent CKD with normophosphatemia and iron deficiency did not decrease serum FGF23 levels. With intact-FGF23 ELISA kit, we measured active FGF23 levels, and with C-FGF23 ELISA kit, we measured, both, active and cleaved C-terminal FGF23. Therefore, serum C-FGF23 levels indicated transcription of FGF23 [27]. Recent studies have showed that iron deficiency promoted the transcription of FGF23 and iron-supplementation decreased serum C-FGF23 levels [22, 25]. In this study, serum C-FGF23 levels were not decreased in the FCH-group and SFC-group, although elevated serum ferritin levels were noted. This is because in the FCH-group, eGFR had decreased in the follow-up period. Serum FGF23 levels increase with decreasing eGFR [3]. Therefore, the effect of iron-supplementation for FGF23 cancelled the effect of decreased eGFR. The reason for decreased eGFR in the FCH-group was the natural course of CKD because the FCH-group had lower eGFR (although not significant) compared with the other groups. Therefore, we analyzed 14 patients of the FCH group except the three patients whose eGFR fell below 10 mL/min/1.73 m^2 during the observational period. In the FCH-group, eGFR had not changed, and serum CFGF23 and iPTH levels were significantly decreased (Table 3). In the SFC-group and control-group, there was no patient whose eGFR fell below 10 mL/min/1.73 m^2.

Another reason why FGF23 was not significantly decreased in FCH-group is severity of iron deficiency. It was reported that in patients with iron deficiency undergoing hemodialysis, administration of FCH decreased serumFGF23 levels and it was independent of the serum phosphate levels [25]. The ferritin level in the report was 25.6 ± 24.3 ng/mLmL, which was lower than the level reported in our study. If patients had severe iron deficiency in the FCH-group, serum FGF23 levels might be decreased too.

In the SFC-group, the elevation of serum ferritin levels was slight but significant compared with the FCH-group. Furthermore, in the FCH-group in which serum ferritin levels were sufficiently elevated, serum C-FGF23 levels had decreased, except the three cases whose eGFR fell below 10 mL/min/1.73 m^2. Therefore, the reason for the non-significant change in serum FGF23 levels in SFC-group may be simple insufficiency of iron-supplementation.

Serum ferritin levels in the SFC-group were not elevated compared with those of the FCH-group. The reason may be the frequency of administration, which was once with each meal in the FCH-group and was once a day in the SFC-group. The efficiency of iron absorption associated with administration frequency of once with each meal was probably superior compared to that of once a day.

Another factor for the decreased serum FGF23 levels in the FCH-group is a reduction of oral phosphate absorption. In the FCH-group, although serum C-FGF23 levels were decreased, serum intact-FGF23 levels were not decreased. The degradation of FGF23 was inhibited due to decreased GFR, although the mechanism is unclear. We estimated that at this level of GFR as seen in our patients, degradation of FGF23 was not inhibited, and transcription of FGF23 was exacerbated by decreased GFR and iron deficiency. Transcription of FGF23, which was exacerbated by iron deficiency, was suppressed with iron supplementation, but intact-FGF23, which is active FGF23, was not decreased. We thought that the reduction of oral

Table 3 Treatment effect of ferric citrate hydrate except 3 cases with eGFR < 10 mL/min/1.73 m^2

$n = 14$	Ferric citrate hydrate		
	Baseline	Week 12	*P*
eGFR (mL/min/1.73 m^2)	25.67 ± 10.63	25.27 ± 9.97	0.1329
iP (mg/dL)	3.41 ± 0.71	3.18 ± 0.77	0.1100
cCa (mg/dL)	9.22 ± 0.25	9.24 ± 0.31	0.5000
Mg (mg/dL)	2.30 ± 0.28	2.39 ± 0.61	0.3943
iPTH (pg/mL)	62.50 (45.75–108.25)	52.00 (41.75–71.75)	0.0123*
iFGF23 (pg/mL)	35.50 (15.86–54.07)	25.50 (17.74–71.93)	0.2131
CFGF23 (RU/mL)	50.30 (32.91–95.30)	35.52 (29.00–51.83)	0.0392*
Fe (μg/dL)	73.50 ± 30.17	72.57 ± 30.81	0.4939
TSAT (%)	22.59 ± 9.63	23.53 ± 8.60	0.2654
Ferritin (ng/mL)	44.00 ± 25.35	76.01 ± 34.31	0.0002*
CRP (mg/dL)	0.24 ± 0.31	0.57 ± 0.85	0.1514
Hb (g/dL)	11.53 ± 1.33	12.16 ± 1.72	0.2866
Plt (10^4/μL)	19.67 ± 4.64	18.88 ± 4.68	0.3517

*$P < 0.05$ compared with baseline

Table 4 Comparison of published studies and our data

Study	Duration	*N*	Character	Binder	Outcome
Oliveira [10]	1.5 months	40	Ccr34.55	CaAc	Compared with CaAc, SCl led to:40% reduction in iFGF23
			iP3.45 ± 0.65	SCl	30% reduction in PTH
Gonzalez-Parra [11]	4 weeks	18	Ccr42.08	LC	Change from baseline after LC: 24% reduction in CFGF23
			iP3.41 (3.2–3.6)		No change in PTH
Block [12]	9 months	148	eGFR32	LC, CaAc, SCO3, placebo	Compared with placebo, iP binders led to: Reduction in iP from a mean of 4.2–3.9 mg/dL
					No reduction in CFGF23
			iP4.2 ± 0.2		iFGF23 reduced with SCO3
Di iorio [13]	1 week	32	eGFR30	LPD	Compared with LPD, VLPD led to: 12% reduction in iP
			iP4.1 ± 0.7	VLPD	34% reduction in iFGF23
					No change in PTH
Chue [14]	9 months	109	eGFR50	SCO3	Compared with placebo, SCO3 led to: No change in iFGF23
			iP3.16 ± 0.53	Placebo	No change in PTH
Seifert [15]	12 months	38	Ccr47	LC	Compared with placebo, LC led to: No change in iFGF23
			iP3.5 ± 0.5	Placebo	No change in PTH
Isakova [16]	3 months	39	eGFR37.8	LC + diet, Placebo + diet, LC, placebo	Change from baseline after 900 mg iP diet-LC led to: 35% reduction in FGF23
			iP3.6±0.7		No change in PTH
Urena-Torres [17]	3 months	29	eGFR42.5	LC	Compared with placebo, LC led to: No change in iFGF23
				Placebo	No change in PTH
Our data	3 months	40	eGFR25.9	FCH	Change from baseline after FCH
			iP3.58 ± 0.68	SFC	No change in FGF23
				Control	Reduction in PTH from a median of 68.0–60.0 pg/mL

phosphate absorption is not efficacy, because intact-FGF23 was not reduced. Although past reports did not show decreased FGF23 levels, the reason why FCH decreased FGF23 levels in patients with iron deficiency was iron supplementation.

Serum intact-PTH levels in the FCH-group had significantly decreased. In the SFC-group, intact-PTH level was not changed; therefore, the effect might be caused not by iron-supplementation but because of phosphate binding of FCH. Recent reports have mostly shown that phosphate binders did not decrease serum PTH levels in patients with normophosphatemia (Table 4). Phosphate balance was maintained by FGF23 and PTH in patients with CKD until the end-stage. Only after the phosphate homeostasis has failed, the effect of phosphate-binders to decrease serum FGF23 and PTH levels is observed. Recent review has shown that the failure of phosphate homeostasis is the state of hyperphosphatemia in patients with CKD [28]. In our study, eGFR at baseline was 22.92 ± 11.38 mL/min/1.73 m^2. It was lower compared with recent reports (Table 4). Therefore, even in normophosphatemia with lower eGFR, phosphate-binder may have decreased serum PTH levels. In eGFR 22.92 ± 11.38 mL/min/1.73 m^2, even with normophosphatemia, phosphate-binders might be effective for CKD-MBD management.

In the SFC-group, decreased platelet count was because of iron-supplementation.

This study has certain limitations. The effect of phosphate from diet was not excluded because we did not evaluate the urine phosphate excretion rate. The baseline characteristics of each group were not the same especially in relation with CRP, hemoglobin, and eGFR. A bigger sample size and suitable randomization are necessary to validate our results.

Conclusion

In patients with normophosphatemia and CKD with iron deficiency, FCH decreased serum intact-PTH levels, although it did not decrease serum FGF23 levels. However, except in patients whose eGFR declined, FCH decreased serum CFGF23 levels.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

Human and animal rights (with IRB approval number) The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the human research committee at our institution (authorization No. E15-16).

Informed consent Informed consent was obtained from all individual participants included in the study.

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