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Research Article

Serum Intact and Total Fibroblast Growth Factor 23 Levels and Iron-related Parameters in Hemodialysis Patients

Kenji Tanaka[1*], Yasuki Motomiya[1], Yoshiteru Kaneko[2], Yuichiro Higashimoto[3] and Tatsuo Yoneda[4]

Abstract

Objective: Fibroblast growth factor (FGF)23 suppresses erythropoiesis and is implicated in iron metabolism. It was investigated whether high levels of FGF23 was associated with hepcidin levels of iron metabolism markers in hemodialysis patients.

Methods: The serum hepcidin, erythroferrone, and intact-FGF23 or total-FGF23 level as well as iron-related parameters at pre-dialysis in 70 hemodialysis (HD) patients was measured and performed a regression analysis.

Results: Each measurement for FGF23, including the intact-/total-FGF23 ratio, correlated strongly with both serum inorganic phosphate and calcium-phosphate product concentrations. Serum hepcidin levels showed a positive correlation with TSAT or serum ferritin concentration. In addition, a negative correlation was found between serum of hepcidin and erythroferrone levels, but no correlation was found between FGF23-related measurements and serum hepcidin levels. Both serum FGF23 levels and erythroferrone levels correlated with erythropoietin-stimulating agent treatment.

Conclusion: It was strongly suggested that both serum phosphate concentrations and calcium-phosphate products were associated with FGF23 production in HD patients. As previously reported, the association between hepcidin and iron metabolism markers was reconfirmed, but a simple linear relationship between

[1]MD, Director, Suiyukai Clinic, 676-1 Kuzumoto-cho, Kashihara, Nara, 634-0007, Japan

[2]PhD, Suiyukai Takada Clinic, 1-26 Nishi-machi, Yamatotakada, Nara, 635-0096, Japan

[3]Professor, Department of Chemistry, Kurume University School of Medicine, 67 Asahimachi, Kurume Fukuoka, 830-0011, Japan

[4]Professor, Unit of Dialysis, Nara Medical University, 840 Shijo-Cho, Kashihara, Nara, 6348521, Japan

[*]**Corresponding Author:** Kenji Tanaka, MD, Director, Suiyukai Clinic, 676-1 Kuzumoto-cho, Kashihara, Nara, 634-0007 Japan.

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hepcidin and FGF23 was not observed even after adjusting FGF23. However, a significant negative correlation between erythroferrone and serum hepcidin levels was confirmed in HD patients.

Key words: FGF23; Hepcidin; Erythroferrone; Hemodialysis; Serology.

Abbreviations: FGF23: Fibroblast growth factor 23; CKD: Chronic kidney disease; HD: Hemodialysis; Pi: Inorganic phosphate; FGFR: FGF receptor; HDF: Hemodiafiltration, ERFE: Erythroferrone; ESA: Erythropoiesis stimulating agent; CFGF23: C-terminal fragment of FGF23; CRP: C-reactive protein; i-FGF23: intact-FGF23; t-FGF23: total-FGF23; i-/t-FGF23 ratio: i-FGF23/t-FGF23 ratio; ADHR: Autosomal-dominant hypophosphatemic rickets; BMP: Bone Morphogenetic Protein.

Background

Fibroblast growth factor 23 (FGF23) was first identified as a novel phosphaturic hormone in rickets in 2000 [1]. A few years later, serum levels of FGF-23 were reported to increase during the clinical stage of chronic kidney disease (CKD) as well as serum Pi values [2,3]. Particularly, in hemodialysis (HD) patients, serum FGF23 levels are known to increase extremely similarly to ng/ml levels and correlate with serum inorganic phosphate (Pi) values [4,5]. The phosphaturic action of FGF23 has been confirmed to be αKlotho-dependent action via FGF receptor 1 (FGFR1) [6].

Meanwhile, Gutierrez et al. reported that serum FGF23 levels were strongly associated with mortality risk in HD patients [7], which was quickly followed by Faul et al. who reported a novel action of FGF23, that is αKlotho-independent action via FGFR4 on cardiomyocytes [8]. Since then, research has focused on whether FGF23 has a role in prevalent complications other than left ventricular enlargement in HD patients, such as anemia, functional iron deficiency, and vascular calcification.

As for iron deficiency, FGF23 expression had been reported to be induced by iron deficiency in both experimental model and patients with genetic rickets [9,10].

Although recent reviews mention the clinical safety of high doses of intravenous iron repletion, the optimal dose in HD patients has not yet been standardized [11,12]. In addition, several reports of iatrogenic hemosiderosis have been published in HD patients [13,14]. Therefore, iron metabolism remains elusive in the clinical setting of HD.

Hepcidin, which is produced mostly in the liver, is a master regulator of iron metabolism. Hepcidin consists of 25 amino acids (2.7 k Dalton) [15], binds to alpha-2-macroglobulin, and circulates in the blood, but due to its low affinity, the non-binding type is the primary component of most of the physiological concentration [16]. Hepcidin is expected to be dialyzed by high-performance dialyzers commonly used in on-line hemodiafiltration (HDF) [17]. In addition, hepatic expression of hepcidin was recently reported to be drastically suppressed by erythroblast factor erythroferrone (ERFE), induced by erythropoietin [18].

However, despite most HD patients being treated with several kinds of erythropoiesis-stimulating agents (ESA), circulating levels of hepcidin have been reported to be conversely

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increased in HD patients [19,20]. In contrast, Farrow et al. first reported the induction of FGF23 expression with iron deficiency in an experimental model [9]. Similar clinical observational studies indicating a possible implication of FGF23 with functional iron deficiency in HD patients have also been published [10,21-24].

Several authors have described serum levels of FGF23 measured by a commercial C-terminal FGF23 assay in terms of total-FGF23 (t-FGF23) [25-27]. Although the N-terminal fragment derived from intact FGF23 (i-FGF23), which is generated simultaneously with C-terminal FGF23 fragment (C-FGF23), is not included in t-FGF23 measured, serum levels of FGF23 measured using commercial C-terminal FGF23 assays as t-FGF23 was also described in this study.

To investigate the role of FGF23 in iron metabolism in HD patients, the differences in serum concentrations was first assessed of relevant parameters such as hepcidin and ERFE between regular HD and on-line HDF. The involvement of FGF23 was then investigated in iron-related parameters, including serum levels of hepcidin, and ERFE.

Participants and methods

Study design

This study design is a cross-sectional observational study of two facilities without intervention.

Participants

This study received approval from the Ethics Committee of Suiyukai (protocol code 014, March 15th, 2019). Written informed consent was obtained from all the participants. Seventy end-stage renal disease patients, i.e, 22 receiving on-line HDF and 48 receiving regular HD, were included and 30 healthy volunteers, 19 women and 11 men, aged 48.3 ± 8.15, were included. Their underlying kidney disease was diabetic nephropathy in 25, chronic glomerulonephritis in 22, nephrosclerosis in 11 and one each with SLE, ANCA and gouty kidney. The primary disease was not known for 9 patients. No patients had a history of transfusion, episodes of gross bleeding from the digestive tract, or liver dysfunction. Twenty-five patients received iron repletion with 40 mg of intravenous saccharated ferric oxide weekly or biweekly. Twenty-eight diabetic patients and 12 patients with a history of coronary revascularization were included. None of the patients were taking hypoxia-inducible factor prolyl-hydroxylase inhibitor. Six patients were taking cinacalcet hydrochloride, six patients taking evocalcet, 22 patients taking etelcalcetide and 34 patients were taking both calcimimetics and VD receptor activators for the treatment of secondary hyperparathyroidism. Five patients had undergone total parathyroidectomy with autografting. Dietary phosphate restriction (18mg/kg/day) was indicative in all patients.

Hemodialysis

HD treatment was performed three times a week for 4 h in every patient, and 42 patients underwent HD with a polysulfone membrane, the rest underwent with cellulose triacetate-based hollow fiber membrane. HDF was performed by pre-dilution method, and substitution volumes varied from 24 to 36 L/session depending on the patient's dry

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weight. Polysulfone membrane were used for hemodiafilter in all cases. The dialysate used in all the patients was acetate-free bicarbonate fluid. The dialysate calcium concentrations were 3.0 mEq/mL.

ESA andiron repletion

Three kinds of ESAs, including epoetin beta, darbepoetin alfa, and epoetin beta pegol, were administered to 57 patients. In this study, based on guidelines [28] and prior research [29,30], the conversion ratio of each ESA dosage was epoetin beta (unit/w): darbepoetin alfa (μg/w)=1:200 and darbepoetin alfa (μg/w): epoetin beta pegol (μg/w)=1:1.2. The weekly doses of darbepoetin alfa and epoetin beta pegol were converted into epoetin β (unit/w) units using the following conversion ratio:

ESA dosage conversion ratio; epoetin β (unit/w): darbepoetin alfa (μg/w): epoetin beta pegol (μg/w)=1: 200: 240

The converted dosage of ESAs administered to 57 patients varied from 7.35 to 249 units/kg/week.

Twenty-five patients received iron repletion using saccharated ferric oxide at a dose of 0.66 to 3.40/ kg/month. Both treatments were administered at the end of the HD session.

Sampling and analytical methods

Blood sampling was performed at pre-dialysis of the beginning of the week, at least 3 days after the injection of ESAs or iron repletion. All samples were stored in -80 ℃ freezer until assay.

Biochemical measurement

All dialysis-related biochemical parameters were measured in the Falco laboratory (Kyoto, Japan). Serum levels of hepcidin, ERFE, i-FGF23, and t-FGF23 were measured at Kurume University using commercially available kits as follows: Hepcidin 25 (bioactive) HS ELISA (DRG Instruments GmbH, Marburg, Germany), human erythroferrone (ERFE) ELISA kit (Intrinsic Lifesciences, La Jolla, CA, USA), Human FGF-23 (Intact) ELISA Kit (Immutopics, San Clemente, CA), and FGF23 (C-terminal) multi-matrix ELISA kit (Biomedica, Vienna, Austria). Serum levels of t-FGF23 were measured using a commercial kit for cFGF23 assay, in which human recombinant C-FGF23 (7.52 kD) was employed as a referral protein and expressed in pg/mL. Therefore, i-FGF23 (32 kD) in serum samples were counted as C-FGF23 (7.52 kD), which may have led to an underestimation of the true measurement values. Thus, the i-/t-FGF23 ratio was calculated in units of molar value, not pg/mL. Log FGF23 levels were adjusted by age, sex, dialysis history, and serum albumin levels to obtain adjusted log FGF23.

Statistical analysis

All data are expressed as mean ± standard deviation or n (%). Statistical comparisons were performed using a two-tailed Student's t-test for normally distributed variables and Wilcoxon rank sum test for non-normally distributed variables. The mean values of i-FGF23, t-FGF23, ERFE, and hepcidin in the three groups were compared using the Tukey-Kramer's method after ANOVA. The Pearson correlation coefficient was used as a measure of the linear between the two sets of data. For

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non-normally distributed variables, the correlation coefficient was obtained using the natural logarithm of these variables. All analyses were performed using JMP version 9.0.0 (University of California, Merced, California, USA). Statistical significance was set at $p<0.05$.

Results

Baseline characteristics and clinical laboratory data are presented in Table 1, while baseline characteristics and relevant routine laboratory biochemistries are presented in Table 2. Serum albumin concentration varied from 3.0 g/dL to 4.4 g/dL. Hemoglobin concentration varied from 8.2 to 16.5 g/dL. Serum C-reactive protein (CRP) values were less than 1.54 mg/dL in all patients. The average serum iron, ferritin, and TSAT values were within the normal range as follows: 72.0 μg/dL, 146.8 ng/mL, and 26.3%, respectively. However, TSAT in 18 patients was less than 20 % and serum ferritin levels were less than 25 ng/mL in 10 patients. Serum Ca concentration (corrected for albumin level) varied from 8.0 to 10.1 mg/dL and serum Pi concentration varied from 2.6 to 9.2 mg/dL. The serum levels of intact PTH varied from 24 to 654 pg/mL.

There were no significant differences between the two patient groups according to relevant parameters in patients on on-line HDF and regular HD, such as KT/V, hepcidin, ERFE, Pi, Ca, Ca/P product, and ESA dose, excluding the i-/t-FGF23 ratio (Table 3). There was a significant difference in the serum ferritin levels, between patients with iv iron repletion and without (200.0 vs 117.3 ng/mL, $p=0.003$).

	ESRD patients (n=70)
Age (years)	70.0 ± 10.6
Female n/N (%)	28/70 (40%)
BMI (kg/m²)	22.8 ± 4.50
Diabetes Mellitus n/N (%)	28/70 (40%)
Hypertension n/N (%)	46/70 (65%)
Ischemic heart disease n/N (%)	12/70 (17%)
Dialysis Vintage (months)	132.2 ± 115.7
Hemodiafiltration n/N (%)	22/70 (31.4%)
Polysulfone membrane n/N (%)	42/70 (60%)
Kt/V	1.26 ± 0.26
Treatment with ESAs n/N (%)	57/70 (81.4%)
Parenteral ferrotherapy n/N (%)	25/70 (35.7%)
Use of phosphate binder n/N (%)	51/70 (72.9%)
Use of VD receptor activators n/N (%)	58/70 (82.9%)
Use of calcium sensing receptor analogs n/N (%)	13/70 (18.6 %)
ESA dose (u/kg/week), N=57	57.2 ± 55.5
Dose of saccharated ferric oxide (mg/week), N=25	9.4 ± 14.5

Table 1: Patient demographics.

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	ESRD patients (n=70)	Healthy volunteers (n=30)	P value
Hemoglobin (g/dL)	10.9 ± 1.30	14.0 ± 1.43	*<0.001
RBC (104/L)	350 ± 48.6	462 ± 45.8	*<0.001
Ht (%)	34.3 ± 4.17	43.3 ± 4.02	*<0.001
Albumin (g/dL)	3.66 ± 0.33	4.56 ± 0.263	*<0.001
Aspartate aminotransferase (IU/L)	14.4 ± 7.43	23.5 ± 9.78	*<0.001
Alanine aminotransferase (IU/L)	12.3 ± 6.96	21.5 ± 10.3	*<0.001
Potassium (mEq/L)	4.90 ± 0.73	4.07 ± 0.343	*<0.001
Urea nitrogen (mg/dL)	65.9 ± 16.2	13.0 ± 3.32	*<0.001
Creatinine (mg/dL)	10.8 ± 2.94	0.726 ± 0.157	*<0.001
Uric acid (mg/dL)	6.05 ± 1.43	5.01 ± 1.40	*0.001
Corrected calcium (mg/dL)	9.02 ± 0.53	9.35 ± 0.316	*0.002
Inorganic phosphorus (mg/dL)	5.36 ± 1.38	3.35 ± 0.366	*<0.001
Iron (μg/dL)	72.0 ± 27.6	99.6 ± 33.8	*<0.001
TSAT	26.3 ± 10.6	27.1 ± 12.2	0.78
Ferritin (ng/dL)	146.8 ± 126.5	90.6 ± 94.4	*0.02
C-reactive protein (mg/dL)	0.19 ± 0.26	0.03 ± 0.06	*<0.001
Hepcidin (ng/mL)	24.3 ± 23.2	9.89 ± 6.03	*0.004
ERFE (ng/mL)	7.52 ± 7.42	8.91 ± 7.02	0.36
t-FGF23 (pmol/L)	88.3 ± 84.2	2.29 ± 3.44	*<0.001
i-FGF23 (pmol/L)	67.2 ± 71.4	0.324 ± 0.463	*<0.001
i-/t-FGF23 ratio	0.686 ± 0.349	0.204 ± 0.267	*<0.001

Table 2: Laboratory data of subjects and comparison of the mean value between ESRD patients and healthy volunteers.

	HD (n=48)	HDF (n=22)	P value
Age (years)	69.4 ± 10.3	71.3 ± 11.3	0.49
Female n/N (%)	19/48 (39.6%)	9/22 (40.9%)	0.92
Dialysis Vintage (months)	136 ± 117	125 ± 116	0.73
Treatment with ESAs n/N (%)	42/48 (87.5%)	15/22 (68.2%)	0.06
Parenteral ferrotherapy n/N (%)	15/48 (31.3%)	10/22 (45.5%)	0.25
Kt/V	1.26 ± 0.28	1.25 ± 0.20	0.9
Inorganic phosphorus (mg/dL)	5.36 ± 1.22	5.35 ± 1.71	0.97
Corrected calcium (mg/dL)	9.04 ± 0.57	8.99 ± 0.44	0.71
C-reactive protein (mg/dL)	0.226 ± 0.296	0.099 ± 0.079	0.25
Hepcidin (ng/mL)	25.6 ± 22.8	21.6 ± 24.4	0.34
ERFE (ng/mL)	8.25 ± 8.46	5.91 ± 4.10	0.2
t-FGF23 (pmol/L)	91.6 ± 84.1	81.1 ± 85.9	0.32
i-FGF23 (pmol/L)	70.0 ± 70.2	61.1 ± 75.0	0.12
i-/t-FGF23 ratio	0.756 ± 0.325	0.534 ± 0.360	*0.01
Treatment with ESAs	42/48 (87.5%)	15/22 (68.2%)	0.05
adjusted log t-FGF23	3.71 ± 0.51	3.62 ± 0.56	0.53
adjusted log i-FGF23	3.12 ± 0.86	3.00 ± 0.98	0.6

Table 3: Comparison of parameters between hemodialysis patients and on-line HDF patients.

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Hepcidin

Serum hepcidin levels varied from 3.5 to 106.4 ng/mL, in HD patients and significantly higher than that in healthy volunteers (24.3 v 9.89, p=0.004). Serum hepcidin levels were positively correlated with both TSAT and Ft (p<0.001 and p<0.001, respectively). No correlation was found between serum hepcidin levels and FGF23 related measurements (Figure 1). However, a marginal correlation could be suggested with the i-/t-FGF23 ratio (p=0.06) (Figure 2). As for hepcidin, iron replacement therapy using saccharated ferric oxide was recognized as a significant confounding factor. (p=0.005) (Additional file 1).

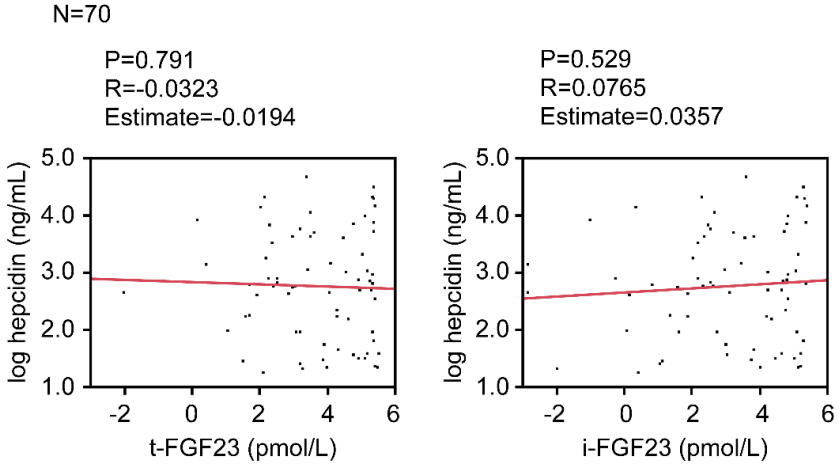

Figure 1: FGF23 vs hepcidin. In 70 ESRD patients, both t-FGF23 and i-FGF23 did not show correlation with log hepcidin.

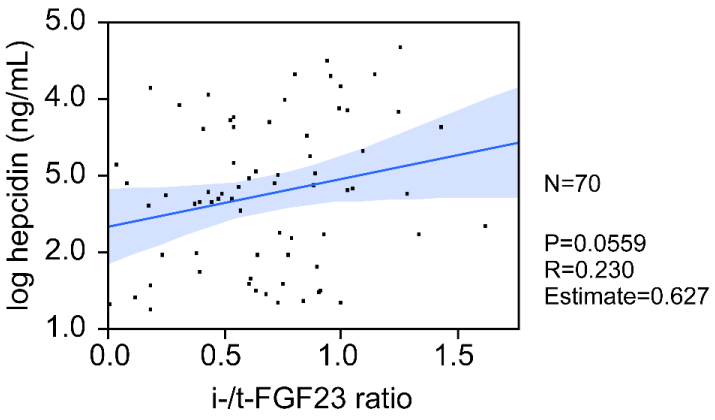

Figure 2: log hepcidin vs i-/t-FGF23 ratio. i-/t-FGF23 ratio: intact-FGF23/ total-FGF23 ratio. In 70 ESRD patients, marginal correlation was suggested between log hepcidin and the i-/t-FGF23 ratio. The 95% confidence intervals of the regression line are colored.

ERFE

Serum ERFE levels varied from 0.8 to 40.9 ng/mL, which was lower than that in healthy volunteers (7.52 v. 8.91), but there was no significant difference (p=0.36). There was no difference in serum ERFE levels between

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patients with and without ESA treatment (7.72 vs 6.62, p=0.634). Thus, correlation with serum hepcidin levels was studied in all patients, and a weak inverse correlation was confirmed (p=0.046, R=-0.239) (Figure 3). In 57 patients receiving ESAs, serum ERFE levels were dependent on the ESA dosage (p = 0.003, R=0.281) (Figure 4). In addition, serum ERFE levels were weakly correlated with both serum i- and t-FGF23 levels (p=0.03, 0.04, R=0.26, 0.24, respectively) (Figure 5). Serum ERFE levels varied from 0.8 to 40.9 ng/mL, which was lower than that in healthy volunteers (7.52 v. 8.91), but there was no significant difference (p=0.36). There was no difference in serum ERFE levels between patients with and without ESA treatment (7.72 vs 6.62, p=0.634). Thus, correlation with serum hepcidin levels was studied in all patients, and a weak inverse correlation was confirmed (p=0.046, R=-0.239) (Figure 3). In 57 patients receiving ESAs, serum ERFE levels were dependent on the ESA dosage (p=0.003, R=0.281) (Figure 4). In addition, serum ERFE levels were weakly correlated with both serum i- and t-FGF23 levels (p=0.03, 0.04, R=0.26, 0.24, respectively) (Figure 5).

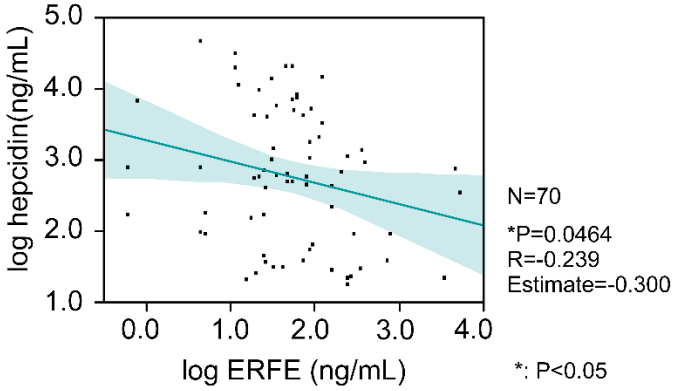

Figure 3: log hepcidin vs log ERFE. In 70 ESRD patients inverse correlation was suggested between log hepcidin and ERFE. The 95% confidence intervals of the regression line are colored.

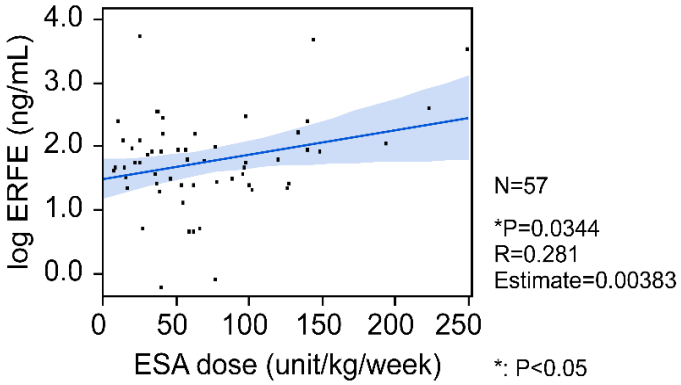

Figure 4: log ERFE vs ESA dose. ESA dose: The converted weekly dose of erythropoietin stimulating agents per body weight. The dose of darbepoetin alfa and epoetin beta pegol were converted into epoetin β (unit/w) units using the conversion ratio. In 70 ESRD patients inverse correlation was suggested between ESA dose and log ERFE. The 95% confidence intervals of the regression line are colored.

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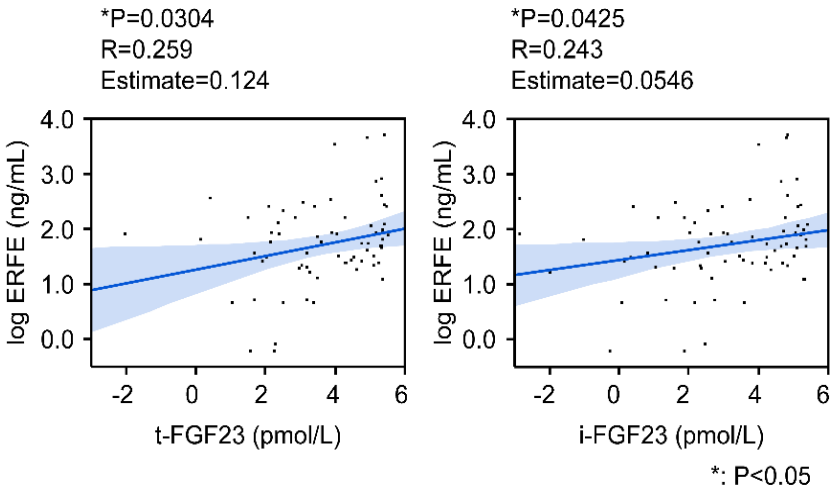

Figure 5: FGF23 vs ERFE. In 70 ESRD patients both t-FGF23 and i-FGF23 showed positive correlation with log ERFE. The 95% confidence intervals of the regression line are colored.

Measurements for FGF23

The serum level of each FGF23 type is presented in Table 2. Serum i-FGF23 levels in ESRD patients varied from 1.5 to 5815 pg/mL, and serum i-FGF23 and t-FGF23 levels in these patients were significantly higher than those in healthy volunteers. The i-/t- FGF23 ratio was higher in regular HD patients (0.756 ±0.325) than in HDF patients (0.534 ±0.360) (p=0.01), both of which were also significantly higher than those in healthy volunteers (0.204 ±0.267) (p<0.001). A strong correlation was observed among these three measurements (Additional file 2). All three measurements showed a strong correlation with the serum Pi levels (Additional file 3). Similarly, i-FGF23 and t-FGF23 correlated with serum Ca levels (p=0.049 and p=0.008, respectively). Consequently, a very strong correlation was found between FGF23-related measurements and calcium-phosphate (CaPi) products (p<0.001, p<0.001, and p=0.02, respectively) (Additional file 4). Neither t-FGF23 nor i-FGF23, however, correlated with serum hepcidin levels (p=0.79, 0.53) (Figure 1). Similar results were obtained after adjusting FGF23 for age, sex, dialysis vintage and serum albumin concentration (p=0.79, 0.53) (Figure are not shown), whereas a marginal correlation was suggested between log hepcidin and the i-/t-FGF23 ratio (p=0.06) (Figure 2).

Multivariate analysis

The underlying mechanisms of both FGF23 and hepcidin production in HD patients are multifactorial, therefore, a multivariate analysis was performed. Among the confounding factors of FGF23, ESAs dosage showed a significant association with t-FGF23 as well as Pi or Ca (Table 4). However, the implication of iron deficiency (TSAT) was not significant.

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	B	SE	β	t	P
Age (years)	-0.0018	0.018	-0.012	-0.1	0.92
Corrected calcium (mg/dL)	1.2	0.33	0.37	3.6	*<0.001
Inorganic phosphorus (mg/dL)	0.79	0.13	0.7	6.2	*<0.001
Kt/V	0.48	0.6	0.082	0.8	0.43
TSAT	-0.01	0.016	0.064	-0.65	0.52
ESA dose (u/kg/week)	0.0065	0.0032	0.22	2.1	*0.04

Table 4: Multivariate analysis of log t-FGF23.

Discussion

FGF23 is produced and cleaved intracellularly mainly in bone cells, and then secreted into circulation in three molecular forms: full-length FGF23 (i-FGF23), N-terminal fragment, and C-terminal fragment of FGF23 (C-FGF23). This cleavage process is considered important for the modulation of physiological actions [9,31]. Nevertheless, no clinical reports specific to C-FGF23 have been published. The term 'total FGF23 (t-FGF23)' was used in this study to describe FGF23 values measured using the FGF23 (C-terminal) multi-matrix ELISA kit. The results of cleaved FGF23 C-fragment (C-FGF23) and full-length i-FGF23 combined with the FGF23 ELISA kit are often referred to as cFGF23, which leads to confusion with the C-terminal fragment of FGF23. In this study, total FGF23 was used to avoid confusion, and the total number of these two peptides was considered, and the mole unit was adopted.

The i-/t-FGF23 ratio was considered to indicate the relative impact of C-FGF23 on i-FGF23. FGF23 is metabolized mainly by the kidneys and increases in CKD. The i-/t-FGF23 ratio was significantly increased in bilateral nephrectomy rats [32]. In experimental studies, Agoro et al. demonstrated that C-FGF23 is capable of blocking FGF23 signaling by i-FGF23 via FGF receptor (FGFR) and ameliorates iron metabolism by reducing hepatic hepcidin expression in CKD mice [33,34], which suggested that i-FGF23 might impair iron metabolism in CKD patients. Conversely, iron deficiency has been reported to induce FGF23 expression via hypoxia-inducible factors in bone cells [35]. However, iron deficiency is generally acknowledged to be closely linked to hepcidin expression. Therefore, a vicious cycle between increased FGF23 levels and impaired iron metabolism via hepcidin production might be suspected in HD patients whose serum levels of FGF23 are extremely persistently elevated. Several clinical studies have suggested a close relationship between high FGF23 levels and iron metabolism disorder as both have been reported in CKD patients [22,24].

It is well known that hepcidin is a master regulator of iron metabolism, but whether

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serum hepcidin levels are linked to functional iron deficiency, even in CKD, remains debatable [36]. Holo-transferrin is known to bind to the Bone Morphogenetic Protein (BMP) 6 receptor and stabilize it along with stimulation of BMP secretion from hepatic sinusoidal epithelia, which leads to hepcidin production [37,38]. Consequently, TSAT generally correlates with serum hepcidin levels. At least in our patients, the association between hepcidin and TSAT and ferritin was reaffirmed.

Then, a subsequent suppressive effect was confirmed by ERFE on serum hepcidin levels.

ERFE has been identified as a specific mediator of ESA and specifically suppresses hepcidin induction by blocking BMP/SMAD signaling [39]. Our study showed a reasonable reciprocal correlation between them, suggesting that the suppressive action of ERFE on hepcidin production was not impaired even under high levels of serum FGF23 found in this study.

Lastly, it was investigated whether FGF23 was implicated in an increase in serum hepcidin levels [17].

However, no significant difference was found between serum hepcidin levels and every measurement with FGF23, including the i-/t-FGF23 ratio, even after adjusting FGF23 for age, sex, dialysis vintage and serum albumin concentration.

Our study indicated no stimulatory effect on hepcidin production by i-FGF23, suggesting a possible inhibitory effect of coexisting C-FGF23 against bioactive i-FGF23, as reported by Agoro et al [33].

Agoro et al. demonstrated the blocking action of exogenous C-FGF23 on production of endogenous i-FGF23 induced by Lipopolysaccharides, which was followed by a distinct reduction in hepatic hepcidin induction and subsequent amelioration of iron disturbance.

Unlike IL-6 and BMP6, to date there has been no report that FGF23 directly stimulates hepcidin production, despite several reports of their close association [33,40]. Therefore, our negative result with hepcidin was considered not to be inconsistent with previous findings.

The lack of correlation of FGF23 with hepcidin might be caused by several factors. Firstly, the amount of bioactive i-FGF23 could not measure in the presence of a receptor blocker, that is, C-FGF23. Second, as shown in Figure 3, serum hepcidin levels should be suppressed by ERFE. In addition, their serum levels were correlated with each other, suggesting that higher FGF23 levels were likely to be associated with higher ERFE levels (Figure 5). As a result, serum hepcidin levels were unlikely to increase due to ERFE-dependent inhibition, irrespective of high i-FGF23 levels. Third, as shown in the multivariate analysis (Table 4), ESAs stimulate FGF23 production. The bone marrow is reported to produce FGF23 as much as osseous tissue and respond so highly to ESA, unlike osseous tissue [41-43]. ESA is known to stimulate FGF23 cleavage as well as production. Thus, substantial amounts of C-FGF23 may be derived from bone marrow [41,44] and the increased C-FGF23 may inhibit against the effect of i-FGF23 on hepcidin. Fourth, increases in serum hepcidin levels

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following iron agent injection may persist even more than three days later in some cases, which might otherwise be lowered to basal levels in two days.

Fifth, VD receptor activators act on the nuclear VD receptor, stimulates the promoter region of the FGF23 gene, and promotes FGF23 production [45]. In addition, calcimimetics was reported to suppress FGF23 production by its PTH suppression effect and serum Ca-lowering effect [46,47]. Therefore, it is quite possible that these drugs used for the treatment of secondary hyperparathyroidism affect FGF23 concentrations and interfere with the association between hepcidin and FGF23. However, in our study, the ratio of using these two drugs in combination was as high as 59%, so it was difficult to adjust the effects of these drugs by statistical methods.

Lastly, serum Pi concentrations have been well known as one of the main contributors to increased FGF23 levels in CKD [48,49]. In HD patients the details remain unclear. However, both the serum Pi concentrations and CaPi products might be the most powerful confounding factor in the correlation between serum levels of FGF23 and hepcidin.

In addition, a recent basic study indicated that Pi activated GALNT3, which governs o-glycosylation of i-FGF23 and protects it from cleaving [50]. Accordingly, our result that the i-/t-FGF23 ratio correlated with serum Pi concentrations and CaPi products, also indicates that these two factors suppress FGF23 cleavage and stimulate FGF23 production.

In our study, hepcidin is not correlated between i-FGF23 concentrations, but a slight possible correlation was suspected between the i-/t-FGF23 ratio, so this ratio may more strongly reflect the effect of FGF23 on hepcidin than the level of i-FGF23.

Therefore, when considering the effect of FGF23 on hepcidin, it may be necessary to pay attention not only to i-FGF23 or t-FGF23 concentrations but also to the i-/t-FGF23 ratio.

Limitation

Our study had several limitations other than the small sample size of the participants studied. First, there was a lack of serum levels specific for C-FGF23. Second, serum hepcidin levels were measured in only one location. Hepcidin is produced from various cells other than hepatocytes, including macrophages and adipocytes.

Therefore, serum hepcidin levels are likely to vary depending on nutrition and microinflammation levels. Third, there is a lack of measurement of high-sensitivity CRP to negate a non-infectious inflammation and lack of assay for soluble transferrin receptors, which are acknowledged to be a sensitive marker for iron deficiency.

Conclusion

It was strongly suggested that both serum phosphate concentrations and calcium-phosphate products were associated with FGF23 production in HD patients. As previously reported, the association between hepcidin and iron metabolism markers was reconfirmed, but a simple linear association

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between hepcidin and FGF23 was not observed even adjusted FGF23. However, a significant negative correlation was confirmed between erythroferrone and serum hepcidin levels in HD patients.

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Author contributions

Conceptualization, KT; methodology, KT, YH; formal analysis, KT; investigation, KT, YM, YK; resources, YM; data curation, KT; writing-original draft preparation, KT; writing-review and editing, YK, TY; supervision, TY.

Ethics declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Suiyukai (protocol code 014, March 15th, 2019). Written informed consent was obtained from all the participants involved in the study.

Competing interests

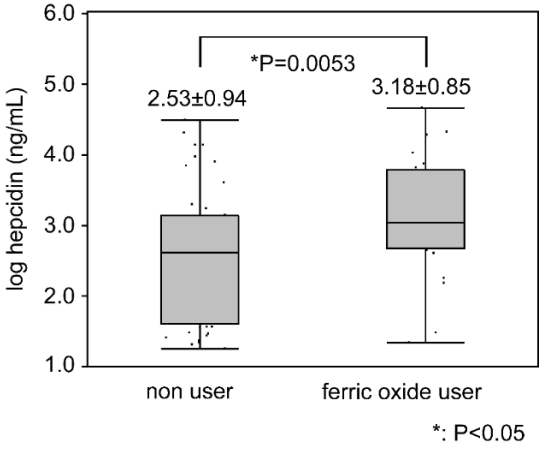
The authors declare no competing interests.

Consent for publication

Not applicable.

Availability data and material

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



Additional file 1: The difference of hepcidin level between ferric oxide user and nonuser. 25 patients have received parenteral ferrotherapy with saccharated ferric oxide 40mg weekly or biweekly intravenously. The ferric oxide users were significantly higher than nonusers in the serum level of hepcidin.

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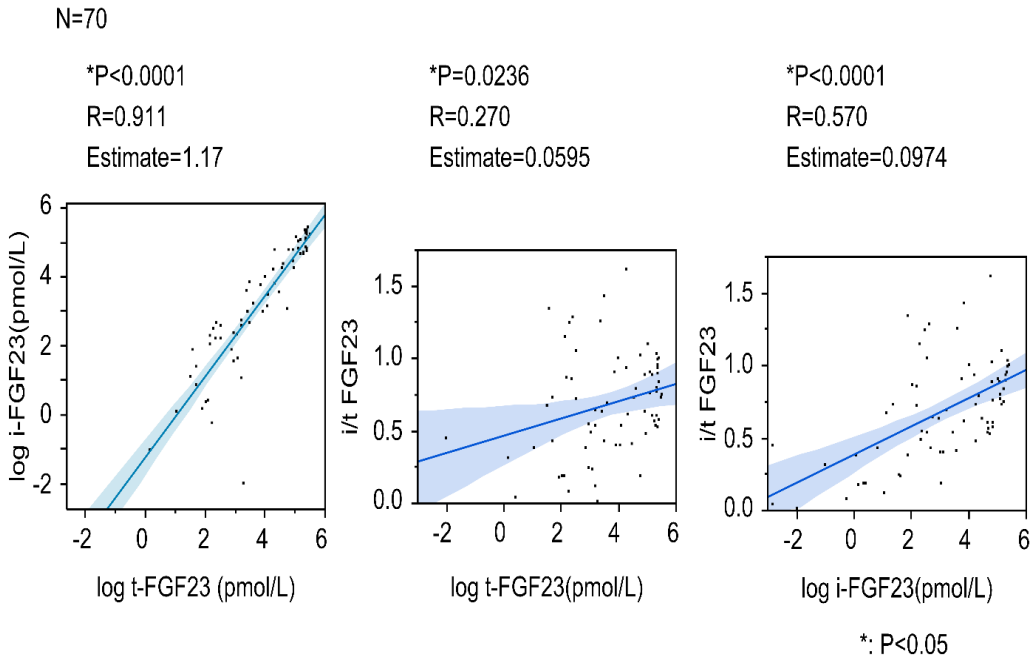
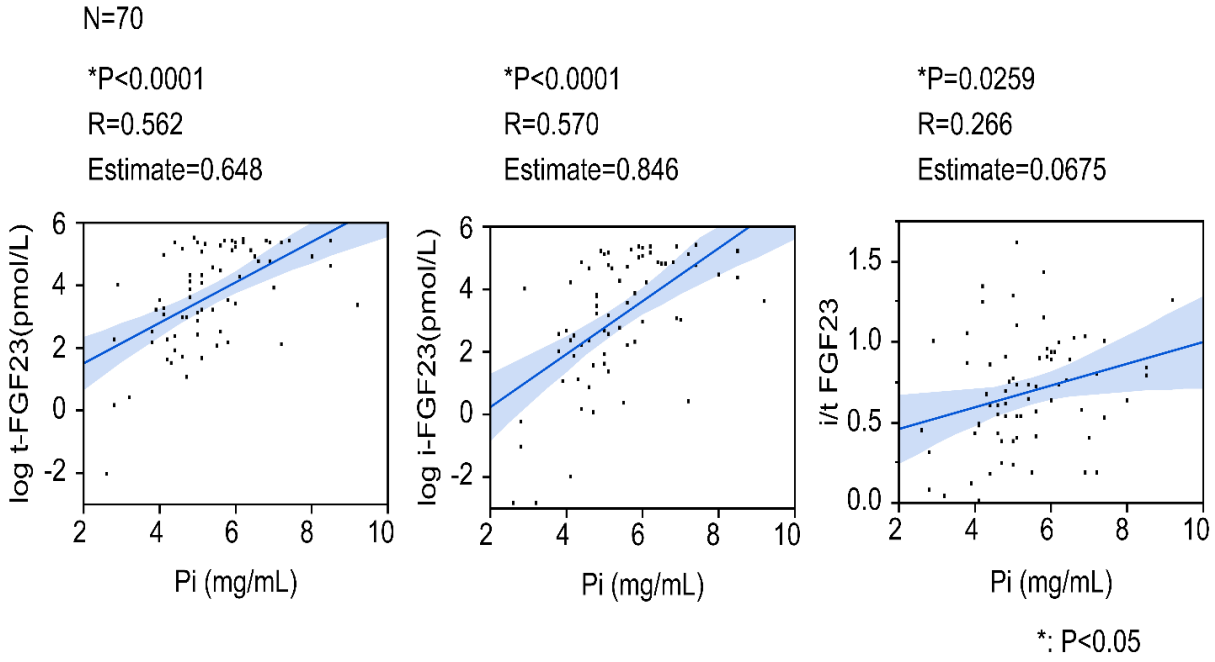


Additional file 2: log i-FGF23 vs log t-FGF23. In 70 ESRD patients, FGF23-related measurements including t-FGF23, i-FGF23 and i-/t-FGF23 ratio showed positive correlation each other. The 95% confidence intervals of the regression line are colored.



Additional file 3: FGF23 vs Pi. In 70 ESRD patients, FGF23-related measurements including t-FGF23, i-FGF23 and i-/t-FGF23 ratio showed positive correlation with serum level of inorganic phosphate. The 95% confidence intervals of the regression line are colored.

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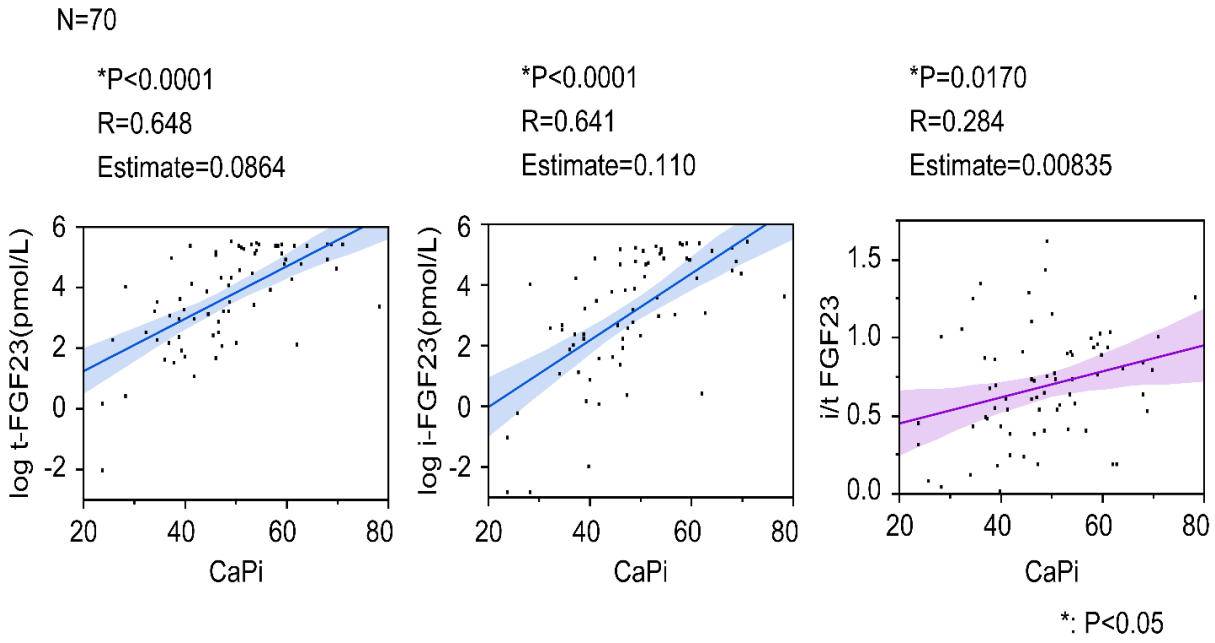

Additional file 4: FGF23 vs CaPi product. In 70 ESRD patients, FGF23-related measurements including t-FGF23, i-FGF23 and i-/t-FGF23 ratio showed positive correlation with calcium-phosphate products. The 95% confidence intervals of the regression line are colored.

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