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Research Article

Serum Levels of the C-terminal Fragment of Fibroblast Growth Factor 23 (C-FGF23) and Hepcidin in Patients with Hemodialysis Undergoing Treatment with a Proline Hydroxylase Domain (PHD) Inhibitor

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Abstract

Background: We previously reported, for the first time, serum levels of the C-terminal fragment of fibroblast growth factor 23 (C-FGF23) in patients undergoing hemodialysis (HD). Most HD patients have undergone treatment with either recombinant erythropoietin (r-EPO) or hypoxia-inducible factor (HIF) proline hydroxylase domain (PHD) inhibitor, both of which stimulate FGF23 production and cleavage.

Methods: This cross-sectional observational study involved analyzing measuring FGF-related parameters and comparing results for subgroups of patients who received either r-EPO and or a PHD inhibitor.

Results: No significant difference was observed for iron-related parameters or serum hepcidin levels in both subgroups of patients. Significant differences were found for certain FGF-23-related parameters.

Conclusion: Both FGF23 production and cleavage were stimulated more in patients treated with the PHD inhibitor than in patients treated with r-EPO.

More Information

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Keywords: Fibroblast growth factor 23; FGF23; C-terminal fragment; Hemodialysis; Hepcidin

Introduction

Currently, most patients undergoing hemodialysis (HD) have been receiving different kinds of treatment with erythropoiesis-stimulating agents (ESAs). These drugs, which are analogous to erythropoietin (EPO) and a inhibitor for the proline hydroxylase domain (PHD) of hypoxia-inducible factor (HIF), have been clinically applied in patients with chronic kidney disease (CKD). The inhibitor stabilizes HIF activity. In other words, HIF activity in patients given the PHD inhibitor may be more sensitive to the presence of ischemic lesions than HIF activity in patients given recombinant EPO (r-EPO). HIF is a transcription factor for many genes in which the coding regions of both EPO and fibroblast growth factor 23 (FGF23) are involved [1,2]. Thus, PHD inhibitors induce constant FGF23 production as well as EPO production. HIF is also believed to be a transcription factor for the furin gene, so that FGF23 undergoes degradation after translation [3]. Therefore, the PHD inhibitor is thought to cause a slight increase in intact full-length FGF23 (i-FGF23) levels compared with increases in C-terminal fragment FGF23 (C-FGF23) levels. EPO also reportedly stimulated both FGF23 production and FGF23 cleavage [4,5].

In addition, ESAs reduce serum hepcidin levels via induction of erythroferrone from erythroblasts [6]. Very recently, C-FGF23 was also suggested to suppress hepcidin production via binding with bone morphogenetic protein (BMP) 2/9, which is believed to competitively block BMP signaling for hepcidin production [7].

Thus, either an increase in C-FGF23 levels or a decrease

in the ratio of the intact full-length FGF23 to total FGF-23 (t-FGF23) (i/t) supposedly causes a concomitant lowering of serum hepcidin levels.

We thus measured serum levels of C-FGF23 and hepcidin and then compared these serum levels in HD patients given r-EPO and HD patients receiving a PHD inhibitor.

Materials and methods

Study design: This study is a cross-sectional clinical investigation.

Subjects

In this study we evaluated two HD patient subgroups as follows: Our study included 18 HD patients undergoing treatment with a PHD inhibitor for more than 1 year and 82 HD patients undergoing treatment with r-EPO. The mean age ± standard deviation (SD) was 69.6 ± 16.7 in 18 patients receiving the PHD inhibitor and 73.5 ± 10.3 years in 82 patients given r-EPO. The primary diseases were nondiabetic in 53% of patients and diabetic in 47% of patients. All patients had HD performed three times per week. The mean ± SD of the single-pool Kt/V was 1.41 ± 0.29 in patients having the PHD inhibitor treatment and 1.30 ± 0.27 in patients given the r-EPO treatment (Supplemental Table 1).

ESA agents and iron repletion

The 18 patients who were refractory to r-EPO treatment received the PHD inhibitor daprodustat, with the dosage dependent on individual hemoglobin concentrations, as follows: daprodustat was administered orally at a daily dosage of 7 mg – 56 mg/week.

Eighty-two patients received three kinds of ESAs as described previously. Five of the 18 patients receiving the PHD inhibitor and 42 of the 82 patients receiving r-EPO underwent biweekly iron repletion therapy with intravenous saccharated ferric oxide.

Laboratory measurements

As previously reported, basic laboratory variables including serum concentrations of iron and ferritin (Ft) were measured at FALCO Biosystems, Ltd (Kyoto, Japan) [8]. The serum levels of i-FGF23 were measured by using the Human FGF23 (Intact) ELISA Kit (Immutopics, Inc., San Clemente, CA, USA), and the serum levels of C-FGF23 were determined by using the FGF-23CT ELISA Kit (Aviscera Bioscience, Inc., Santa Clara, CA, USA). Serum levels of bioactive hepcidin were measured at Kurume University by using commercial kits (DRG Instruments GmbH, Marburg, Germany), and serum levels of soluble transferrin receptor (sTfR) were ascertained similarly by using commercial kits (Abcam plc, Cambridge, UK) [9].

Supplemental Table 1: Clinical and biochemical features of patients.

Characteristic	ESA patients (n = 82)	HIF-PHD patients (n = 18)
Age (years)	73.5 ± 10.3	69.6 ± 16.7
Female, n/N (%)	37/82 (45.1)	8/18 (44.4)
Body mass index	22.2 ± 4.2	22.5 ± 4.1
Dialysis vintage (months)	119.0 ± 110.8	67.9 ± 94.3
Diabetic, n/N (%)	34/82 (41.5)	13/18 (72.2)
Hemodiafiltration, n/N (%)	24/82 (29.3)	3/18 (16.7)
Use of polysulfone membrane, n/N (%)	47/82 (57.3)	16/18 (88.9)
Single pool Kt/V urea	1.30 ± 0.27	1.41 ± 0.29
Parenteral ferrotherapy, n/N (%)	42/82 (51.2)	5/18 (27.8)

Data are means ± SD or n/N (%).
ESA: Erythropoiesis-Stimulating Agent; HIF-PHD: Hypoxia-Inducible Factor Proline Hydroxylase Domain

Statistical analysis

All data are expressed as a mean ± standard deviation (SD) or n (%). Statistical comparisons were performed by using a two-tailed Student's t-test for normally distributed variables and a Wilcoxon rank sum test for non-normally distributed variables. The Pearson correlation coefficient was used as a measure of the linear relationship between two sets of data. For non-normally distributed variables, the correlation coefficient was obtained via the natural logarithm of these variables. All analyses were performed with JMP version 9.0.0 (University of California, Merced, CA, USA). The statistical significance was set at $p < 0.05$.

Results

Baseline laboratory data

Table 1 provides baseline laboratory data for the two subgroups of patients. The mean corrected calcium value was 9.02 mg/dL in patients given the PHD inhibitor and 9.01 mg/dL in patients 9.01 given r-EPO, and the mean serum inorganic phosphate (P_i) concentrations were 5.13 mg/dL in patients given the PHD inhibitor and 5.27 mg/dL in patients given r-EPO.

Iron-related parameters

Table 2 presents values of iron-related parameters and sTfR. Serum sTfR levels were 1468.1 ± 755.1 ng/mL in patients given the PHD inhibitor and 1384.9 ± 547.4 ng/mL in patients given r-EPO (p = 0.589). Serum sTfR/log Ft ratio values were 315.7 ± 170.4 in patients given the PHD inhibitor and 299.0 ± 143.4 in patients given r-EPO (p = 0.667). No

Table 1: Baseline laboratory data for patients in this study.

Variable	ESA patients (n = 82)	HIF-PHD patients (n = 18)
Hemoglobin (g/dL)	10.7 ± 0.99	11.1 ± 0.63
Albumin (g/dL)	3.64 ± 0.32	3.61 ± 0.31
Urea nitrogen (mg/dL)	63.9 ± 15.1	66.8 ± 11.2
Creatinine (mg/dL)	10.04 ± 2.52	9.47 ± 2.51
Corrected calcium (mg/dL)	9.01 ± 0.45	9.02 ± 0.43
P_i (mg/dL)	5.27 ± 1.32	5.13 ± 1.08
C-reactive protein (mg/dL)	0.21 ± 0.31	0.22 ± 0.41

ESA: Erythropoiesis-Stimulating Agent; HIF-PHD: Hypoxia-Inducible Factor Proline Hydroxylase Domain; P_i: inorganic Phosphorus

Table 2: Iron-related parameters.

Variable	ESA patients (n = 82)	HIF-PHD patients (n = 18)
Iron (μg/dL)	70.2 ± 25.3	73.8 ± 18.0
Ft (ng/dL)	177.0 ± 126.8	150.6 ± 95.9
TSAT (%)	29.8 ± 10.5	25.3 ± 6.1
sTfR (ng/mL)	1384.9 ± 547.4	1468.1 ± 755.1

ESA: Erythropoiesis-Stimulating Agent; HIF-PHD: Hypoxia-Inducible Factor Proline Hydroxylase Domain; Ft: Ferritin; TSAT: Transferrin Saturation; sTfR: soluble Transferrin Receptor.

significant difference was observed for each parameter in both subgroups of patients.

Hepcidin

Serum hepcidin levels were 22.93 ± 15.06 ng/mL in patients given the PHD inhibitor and 29.26 ± 25.00 ng/mL in patients given r-EPO. The serum hepcidin levels were lower in the former group but were not significantly different from levels in the latter group (p = 0.304).

As well known, serum hepcidin levels are highly correlated with serum Ft concentrations, which this study found as well (Supplemental Figure 1).

FGF23–related parameters

Table 3 presents FGF-23-related parameters. Serum levels of i-FGF23 and i/C ratio in the two groups were not significantly different, but significant differences were found in serum levels of other parameters including t-FGF23, C-FGF23, i/t ratio, and intact FGF23/C-terminal fragment of FGF23 and i/t ratio. Serum t-FGF23 levels in patients given the PHD inhibitor was double those in patients given r-EPO, and serum C-FGF23 levels in patients given the PHD inhibitor was nearly triple those in patients given r-EPO (p < 0.001 and p < 0.001, respectively). The i/t ratio, i.e., an inverse index of the ratio of FGF23 cleavage, in patients given the PHD inhibitor was nearly half of that in patients given r-EPO (p = 0.017) (Figures 1-3).

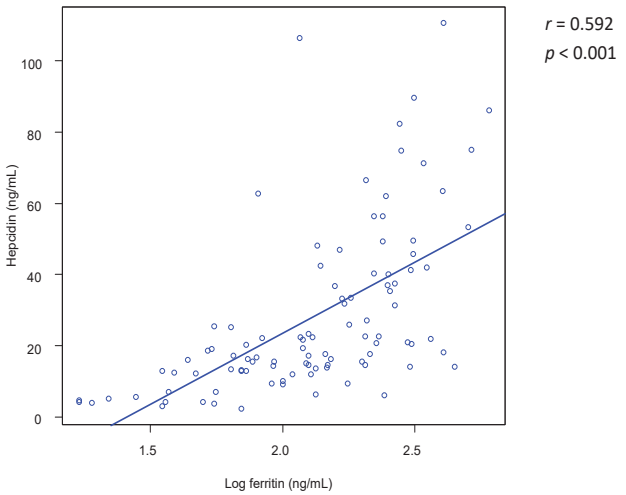
C-FGF23 and hepcidin

Recent experimental studies have indicated that C-FGF23 suppressed hepcidin production [7,9]. Therefore, we investigated the correlation between serum levels of C-FGF23 and hepcidin in all patients in this study. As Supplemental Figure 2 shows, we found a possible inverse correlation, albeit not significant (r = -0.177, p = 0.078).

We also studied the correlation with sTfR and sTfR/log Ft. However, we found no significant correlation (r = 0.088, p = 0.078 and r = 0.054, p = 0.591, respectively; data not shown).

Discussion

Recent experimental studies have indicated that FGF23 directly suppressed hematopoiesis in bone marrow and presumably dysregulated iron metabolism [10]. FGF23



Supplemental Figure 1: Correlation between serum levels of hepcidin and log Ft.

Table 3: FGF23-related parameters.

Variable	ESA patients (n = 82)	HIF-PHD patients (n = 18)	p value
C-FGF23 (pg/mL)	321.3 ± 216.8	963.8 ± 206.5	< 0.001
C-FGF23 (pmol/L)	42.7 ± 28.8	128.2 ± 27.5	< 0.001
i-FGF23 (pg/mL)	1617.8 ± 2087.8	2162.0 ± 2867.0	= 0.353
i-FGF23 (pmol/L)	57.8 ± 74.6	77.2 ± 102.4	= 0.353
t-FGF23 (pmol/L)	100.5 ± 88.9	205.4 ± 99.3	< 0.001
i/C FGF23 ratio	1.70 ± 2.65	0.66 ± 0.88	= 0.105
i/t FGF23 ratio	0.43 ± 0.27	0.26 ± 0.28	= 0.017

FGF23: Fibroblast Growth Factor 23; ESA: Erythropoiesis-Stimulating Agent; HIF-PHD: Hypoxia-Inducible Factor Proline Hydroxylase Domain; C-FGF23: C-terminal Fragment of Fibroblast Growth Factor 23; i-FGF23: intact full-length Fibroblast Growth Factor 23; t-FGF23: total Fibroblast Growth Factor 23; i/C: intact FGF23/C-terminal Fragment of FGF23; i/t: intact/total FGF23.

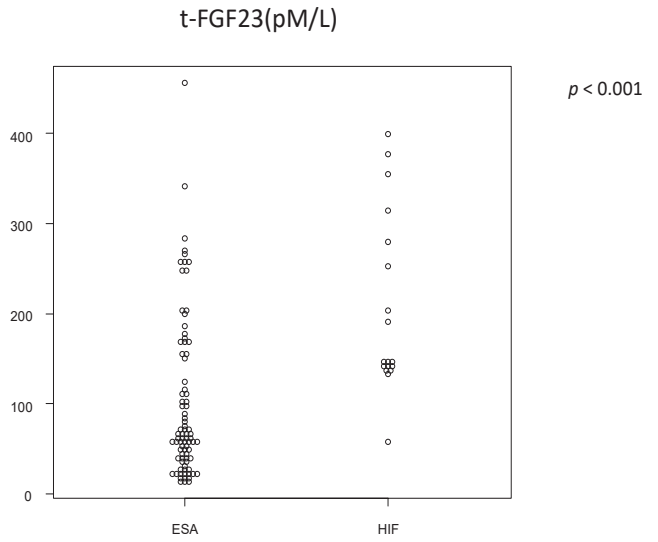
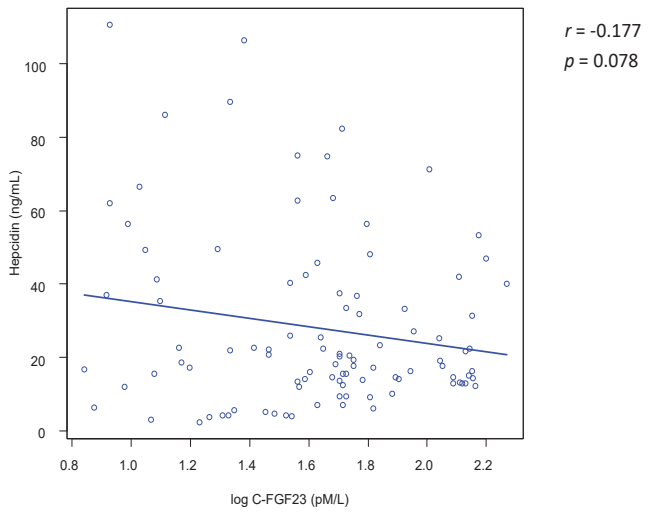


Figure 1: Serum t-FGF23 levels. t-FGF23: total Fibroblast Growth Factor-23; Erythropoiesis-Stimulating Agent; HIF: Hypoxia-Inducible Factor

undergoes intracellular degradation by means of post-translational cleavage at the Arg176XXArg179 site, after which three species, i.e., i-FGF23, the N-terminal fragment, and C-FGF23, are generated and secreted into the circulation. Until quite recently, the two latter species have been thought to be biologically inactive, but recent experimental studies



Supplemental Figure 2: Correlation between serum levels of hepcidin and log C-FGF23. C-FGF23: C-terminal Fragment of Fibroblast Growth Factor 23

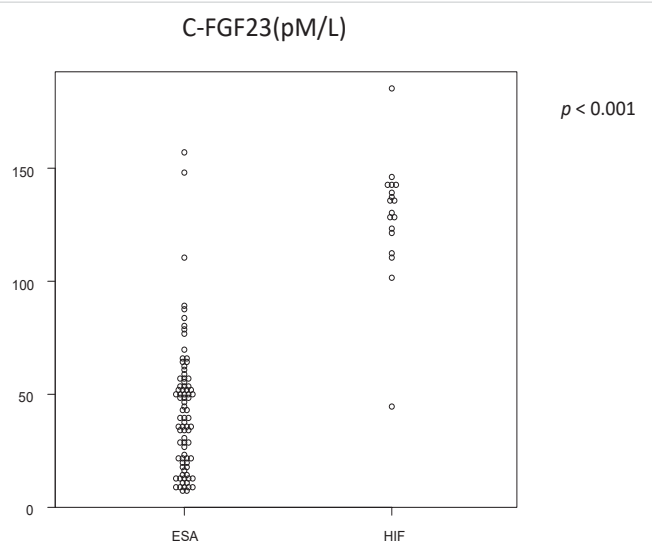


Figure 2: Serum C-FGF23 levels. C-FGF23: C-terminal Fragment of Fibroblast Growth Factor 23; Erythropoiesis-Stimulating Agent; HIF: Hypoxia-Inducible Factor

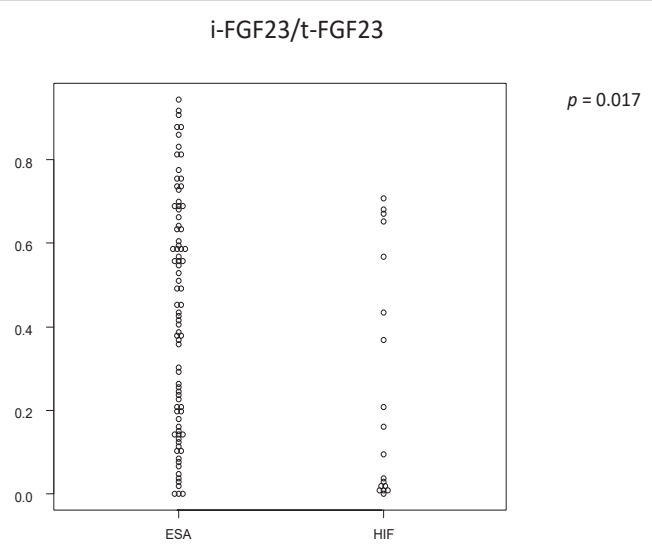


Figure 3: Serum i-FGF23/t-FGF23 ratio. i/t-FGF23: intact/total Fibroblast Growth Factor 23; ESA: Erythropoiesis-Stimulating Agent; HIF: Hypoxia-Inducible Factor

have demonstrated that C-FGF23 does indeed have biological activity in that it blocks FGF23 signaling, but this activity has not yet been proved in clinical studies of patients undergoing HD [7,11,12].

It thus seems quite important to understand whether these two types of ESAs make a difference in the serum levels of C-FGF23 and the i/t ratio, i.e., an inverse index of the FGF23 cleavage ratio, in HD patients.

Goetz, et al. reported that C-FGF23 inhibited a complex formation of FGF23-FGFR-Klotho in experimental models, [11]. Agoro, et al. then demonstrated that C-FGF23 ameliorated iron metabolism hampered by hepcidin, which is a major causative factor in the functional iron deficiency in HD patients [12]. In addition, quite recently, Courbon, et al. reported that C-FGF23 showed an affinity for BMP and inhibited BMP signaling, which is known as a main route for hepcidin production [7].

FGF23 cleavage has reportedly been impaired in patients with renal failure, and our previous study demonstrated that FGF23 cleavage was reduced by as much as 56%, even in HD patients treated with EPO [8]. Therefore, in this study, we measured the serum levels of i-FGF23, C-FGF23, i/C ratio, i/t ratio, and hepcidin in 18 HD patients treated with an HIF inhibitor, and we compared these results with previous results in HD patients treated with r-EPO.

As shown by a high correlation of hepcidin with serum Ft concentration (Supplemental Figure 1) and sTfR index, hepcidin is believed to be a key factor in iron metabolism in HD as well as in other anemic diseases [9]. Hepcidin inhibits iron trafficking via regulation of ferroportin expression on cell membranes [9].

Because hepcidin is mostly excreted via the kidneys, its serum levels are elevated in CKD patients [13]. In addition, hepcidin production in the liver has reportedly been induced by various factors such as endotoxin, pro-inflammatory cytokines, and iron loading, which are likely to be associated with long-term HD [14,15].

In addition, FGF23 has reportedly been a pro-inflammatory factor by itself, which suggests that FGF23 could directly induce hepcidin production in hepatocytes and/or macrophages [16].

Although no clinical report suggesting a direct correlation of hepcidin with FGF23 has yet been reported, hepcidin production is well-known to vary along with iron dysregulation in CKD patients [9].

EPO, however, has been known to directly induce both FGF23 production and its cleavage in bone and/or bone marrow. A study by Flamme, et al. indicated that a PHD inhibitor also induced FGF23 production and cleavage via EPO [17].

In our study, although we found higher levels of serum C-FGF23 in patients receiving the PHD inhibitor than those in patients receiving r-EPO, we did not find a significant difference in both serum hepcidin levels and the sTfR/log Ft ratio. It thus remains unclear whether C-FGF23 reduced hepcidin production via inhibiting BMP signaling and improved iron metabolism by binding with BMP in this clinical setting.

Our study did demonstrate, however, the different effects of the two ESAs on FGF23 production and cleavage. Our previous study indicated clearly that the cleavage rate of the FGF23 (i/t ratio) depended on serum P_i concentrations and that an increase of 10 mg/L in serum P_i concentrations corresponded to about a 10% decrease in the cleavage rate [8]. However, in this study the serum P_i concentration was almost the same in both subgroups of patients. Therefore, a higher cleavage rate in patients given the PHD inhibitor was supposedly due to two possible differences: either the weekly area under the curve value of serum EPO concentrations associated with administration of two

ESAs or biological activity occurred between endogenous EPO induced by the PHD inhibitor and r-EPO.

FGF23 production and cleavage in erythroblasts via EPO were reportedly regulated via the EPO receptor [18]. Given that endogenous EPO has a higher affinity for the EPO receptor than does r-EPO, we believe that our results are reasonable.

In addition, before secretion FGF23 is post-translationally modified by *N*-acetylgalactosaminyltransferase 3 (GALNT3), which prohibits cleavage of FGF23 by furin [19]. High EPO levels had reportedly suppressed expression of this transferase [20]. Therefore, endogenous EPO supposedly suppressed glycosylation more effectively than did r-EPO.

Conclusion

Here, we showed a definite difference in both FGF23 production and FGF23 cleavage between a PHD inhibitor and r-EPO derivatives by selective measurement of the C-FGF23. Although we did not confirm concomitant lower levels of serum hepcidin in patients given the PHD inhibitor in this study, a larger, more expansive study with more patients and longer observation periods is anticipated to show a difference in serum hepcidin levels between the two subgroups of patients who receive ESA therapy.

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