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Association of erythropoietin resistance and fibroblast growth factor 23 in dialysis patients: Results from the Japanese Dialysis Outcomes and Practice Patterns Study

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Abstract

Background: Fibroblast growth factor 23 (FGF23) plays an important role in chronic kidney disease (CKD)-related mineral and bone disorders. High FGF23 levels are associated with increased risk of anaemia in non-haemodialysis CKD patients. FGF23 also negatively regulates erythropoiesis in mice. We hypothesized that higher FGF23 levels are associated with increased erythropoietin hyporesponsiveness among haemodialysis patients.

Methods: The study included 1044 patients from the Japanese Dialysis Outcomes and Practice Patterns Study (J-DOPPS) phase 5 (2012-2015). The outcome was erythropoiesis-stimulating agent hyporesponsiveness (ESA-hypo), defined as mean Hgb <10 g/dL and standardized mean ESA dose >6000 u/week over 4 months following FGF23 measurement. The association between ESA-hypo and FGF23 was estimated using multivariable-adjusted logistic generalized estimating equation regression models.

Results: Patients with higher levels of FGF23 were younger and had higher levels of serum albumin, creatinine, albumin-corrected calcium, phosphorus, PTH, 25(OH)-vitamin D, and had higher percentages of intravenous (IV) iron, IV vitamin D and cinacalcet use. ESA-hypo was present in 144 patients (13.8%). Compared with the third quintile of FGF23 levels, the odds ratio (95% CI) of ESA-hypo was 2.14 (0.99, 4.62) and 1.74 (0.74, 4.11) for the first and fifth quintiles, respectively.

Conclusion: The lowest and highest levels of FGF23 were associated with higher odds of ESA-hypo in patients on maintenance haemodialysis, although the associations were not statistically significant. The relationship between FGF23 and anaemia,

and particularly the increased risks of ESA-hypo at low FGF23 levels which might be the result of energy saving, must be confirmed in larger clinical studies.

KEYWORDS
anaemia, erythropoietin hyporesponsiveness, fibroblast growth factor 23, haemodialysis, haemoglobin

Anaemia with erythropoiesis-stimulating agent (ESA) hyporesponsiveness is a common problem that has been associated with increased mortality in haemodialysis patients.[1] Many factors affect the response to ESA, including iron deficiency, inflammation and malnutrition. For example, iron therapy improved ESA response in iron-deficient haemodialysis patients.[2] Inflammatory and nutritional markers as captured by the malnutrition-inflammation complex score were associated with ESA response in a study of 754 haemodialysis patients.[3] Relatively minor increases in inflammation also predicted ESA hyporesponsiveness in haemodialysis patients.[4]

Fibroblast growth factor 23 (FGF23) is secreted mainly by osteocytes in bone and appears to play a role in activation of vitamin D and in the regulation of serum phosphate and parathyroid hormone (PTH).[5] In addition to its effects on mineral homeostasis, in vivo and in vitro studies suggest that FGF23 plays a role in renal anaemia. In mice, inflammation and functional iron deficiency stimulated FGF23 production.[6] FGF23 suppressed erythropoiesis in mice,[7] and inhibition of FGF23 signalling stimulated erythropoiesis and ameliorated iron deficiency in a mouse model of renal failure with anaemia.[8] Conversely, erythropoietin increased bone marrow and plasma FGF23 levels in mice and in patients with acute kidney injury or chronic kidney disease (CKD).[9,10] FGF23 levels were associated with low haemoglobin levels and risk of developing anaemia in patients with non-dialysis CKD.[11-13] The association between FGF23 levels and ESA hyporesponsiveness among haemodialysis patients has not been well studied. We examined whether FGF23 levels are associated with erythropoietin resistance among Japanese haemodialysis patients.

SUMMARY AT A GLANCE

The study included 1044 patients in Japan from J-DOPPS and found that the lowest and highest levels of serum FGF-23 were associated with increased odds of ESA-hyporesponsiveness in patients on maintenance haemodialysis, though this did not reach statistical significance. Further study is needed to address the relationship between circulating FGF-23 and anaemia in dialysis patients.

1 | MATERIALS AND METHODS

1.1 | Population and data source

The Dialysis Outcomes and Practice Patterns Study (DOPPS; http://www.dopps.org) is an international prospective cohort study of HD practices ongoing since 1996. At the start of each study phase, DOPPS enrolls random samples of patients from stratified, national random samples of dialysis facilities, with departing patients replaced as described previously.[14,15] We examined data from the Dialysis Outcomes and Practice Patterns Study in Japan, phase 5 (J-DOPPS 5; 2012-2015). Study approval was obtained from a central institutional review board and by national and local ethics committees as required, and written, informed consent was obtained from all participants.

An ancillary study to J-DOPPS 5 collected annual biosamples for supplemental laboratory assays that included FGF23.[16] FGF23 levels were obtained from stored serum samples at 1-year intervals using an automated chemiluminescence immunoassay (Hitachi Chemical Diagnostics Systems Co., Ltd., Tokyo, Japan; formerly known as Kyowa Medex Co., Ltd.), which detects the full-length, biologically intact FGF23 molecule (assay range: 5 to 10 000 pg/mL).[17] Initial FGF23 samples were collected an average of 36 days after J-DOPPS 5 study entry (range: 29-47 days).

During a baseline period defined as the 4 months prior to initial FGF23 measurement, demographic and baseline clinical status variables were collected via questionnaire. These were supplemented by laboratory test values and records of renal medications. The outcome period was defined as the 4 months after initial FGF23 measurement, during which laboratory test values and renal medications were recorded monthly. We included patients recruited into this ancillary study who were prescribed HD at a frequency of three times per week for at least 4 months (n = 1169). We excluded patients that died within 4 months of initial FGF23 measurement, had implausible FGF23 measurements, were not prescribed an ESA at baseline, had missing outcome variables, or had HIV. The final analysis sample included 1044 patients.

1.2 | Statistical analyses

1.2.1 | Primary exposure

The primary exposure of interest was FGF23 level. Study subjects were divided into quintiles based on the FGF23 value at the initial sampling: first quintile, 5-440 pg/mL; second quintile, 441-1260 pg/

mL; third quintile, 1261-3420 pg/mL; fourth quintile, 3421-8620 pg/mL; fifth quintile, 8621-76 000 pg/mL.

1.2.2 | Primary outcome

The primary outcome of interest was ESA hyporesponsiveness (ESA-hypo) in the outcome period defined as the 4 months after FGF23 measurement. Following an earlier study by Hasegawa, ESA hyporesponsiveness was dichotomously defined as the combination of mean Hgb <10 g/dL and standardized mean ESA dose >6000 u/week (hereafter referred to as ESA-hypo).[16] We also measured the ESA resistance index (ERI)[18,19] in the outcome period, calculated as:

$$\text{ERI} = \text{mean ESA dose}\,(\text{u/week}) / [\text{dry weight}\,(\text{kg}) \times \text{mean Hgb}\,(\text{g/dL})]$$

where the dry weight was the post-dialysis bodyweight averaged across three dialysis sessions. For given values of mean Hgb and dry weight, higher ERI values indicate a greater ESA dose requirement. Because single-month ESA and Hgb values may not reflect the "usual" or targeted values, we defined ERI on the basis of the average of monthly ESA doses and Hgb values during the outcome period.

Erythropoietin stimulating agent prescription was obtained monthly and standardized to a weekly dose. ESA used to treat anaemia in Japan includes "short-acting" epoetin alfa (and certain biosimilars), "long-acting" darbepoetin alfa and pegylated epoetin beta. To standardize the ESA dose between these different preparations, we converted pegylated epoetin beta doses to darbepoetin alfa using a 1.2:1 ratio[20] and converted darbepoetin alfa doses to epoetin alfa using a 250:1 ratio.[21]

1.2.3 | Covariates

The following covariates were assessed during the baseline period: age, sex, body mass index, years on dialysis (vintage), comorbidities (coronary artery disease, other cardiovascular disease, cerebrovascular disease, congestive heart failure, diabetes, hypertension, cancer other than skin, and parathyroid surgery), cinacalcet use, residual kidney function (self-reported urine output >200 mL/day), and the (blood or serum) levels of albumin, transferrin saturation (TSAT), ferritin, haemoglobin, creatinine, phosphorus, C-reactive protein (CRP), parathyroid hormone, white blood count, platelet count and normalized protein catabolic rate (PCR).

1.2.4 | Analysis models

We estimated odds ratios (with 95% confidence intervals [CI]) for the binary ESA-hypo outcome by FGF23 quintile using logistic generalized estimating equation regression models, with an exchangeable working covariance matrix to account for within-facility patient clustering. We estimated the association (ratios of the means with 95% CI) between log-transformed ERI and FGF23 using linear mixed regression models with a random intercept for each study facility. For each outcome, we estimated the effect of FGF23 with increasing levels of covariate adjustment in three models to assess confounding effects (see footnote in Figure 1). Because patients started with low ESA dose (ESA < 6000 units/week) and low hb (hb < 10 g/dL) may not develop ESA hyporesponsiveness, therefore, we performed a sensitivity analysis, excluding those patients in models. Missing data were multiply imputed using chained equations and results from 20 imputations were pooled using Rubin's formula.[22] Analyses were conducted with SAS 9.4 (SAS Institute, Cary, North Carolina).

2 | RESULTS

Table 1 shows patient characteristics by FGF23 quintile. Patients with higher levels of FGF23 were more likely to be younger and female; had higher body mass index, serum albumin, creatinine, albumin-corrected calcium, phosphorus, PTH, 25 (OH)-Vitamin D; and were more likely to be prescribed IV iron, IV Vitamin D and cinacalcet.

ESA-hypo was observed in 144 patients (13.8%) (Table 2), with the highest proportions in the first and fifth quintiles of FGF23. The median ERI was also highest in the first quintile of FGF23 (Table S1 [data table for Figure 2]). The median [interquartile range] ERI was 20.7 [16.3, 28.3] in patients with ESA-hypo and 8.3 [5.3, 13.4] in patients without ESA-hypo.

Figure 1 and Table S1 show the relationships between ESA-hypo (top panel) or ERI (bottom panel) and baseline FGF23 levels. In a model adjusted for age, sex, dialysis vintage, body mass index and 8 summary comorbidities, we observed numerically higher odds of ESA-hypo for patients below the third quintile of FGF23 (OR = 2.02, 95% CI = 1.13, 3.62 for Q1 vs Q3; and OR = 1.35, 95% CI = 0.75, 2.42 for Q2 vs Q3; model 2) and for patients above the third quintile for FGF23 (OR = 1.69, 95% CI = 0.95, 2.99 for Q5 vs Q3; and OR = 1.13, 95% CI = 0.60, 2.12 for Q4 vs Q3; model 2). These associations were not substantially altered by additional adjustment for other potential confounders (model 3). ERI had little association with FGF23 quintiles in all models (min/max OR vs Q3, 0.99-1.05; model 2). Sensitivity analysis excluding patients with low ESA dose and low hb had similar results (Figure S1).

3 | DISCUSSION

As far as we know, this is the first study to examine the association between ESA hyporesponsiveness and FGF23 levels in a relatively large cohort of haemodialysis patients. We found that the lowest and highest levels of FGF23 were associated with ESA hyporesponsiveness in patients on maintenance haemodialysis. The finding that more ESA hyporesponsiveness is associated with high FGF23 levels is consistent with the reported association among non-haemodialysis CKD patients. However, our study also observed ESA hyporesponsiveness in patients with low FGF23 levels, which has not been reported previously. This

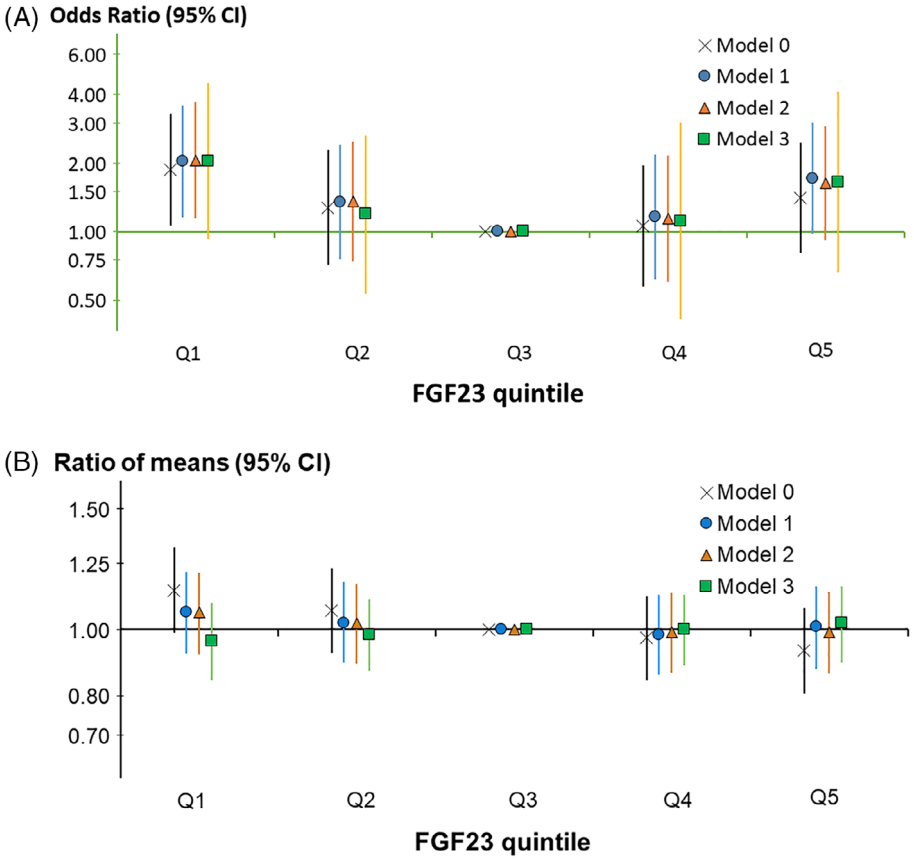

FIGURE 1 Association between ESA hyporesponsiveness or erythropoietin resistance index and baseline serum FGF23 level. A, ESA hyporesponsiveness (ESA-hypo). B, Erythropoietin resistance index (ERI). Model 1: accounting for facility clustering, adjust for age, sex, vintage and body mass index. Model 2: adjusted for model 1 + 8 summary comorbidities. Model 3: adjusted for model 2 + albumin, TSAT, ferritin, haemoglobin, creatinine, residual kidney function, phosphorus, CRP, PTH, cinacalcet use, white blood count, platelet count and normalized PCR. Ca, calcium; CRP, C-reactive protein; FGF23, fibroblast growth factor 23; IV, intravenous; PCR, protein catabolic rate; PTH, parathyroid hormone; TSAT, transferrin saturation

U-shaped association was not observed in non-haemodialysis CKD patients and does not support our hypothesis that only high FGF23 promotes ESA resistance.[12,13]

The lowest quintile of FGF23 in our study had lowest serum phosphorus and PTH levels: thus, low serum phosphorus levels may have suppressed PTH secretion and resulted in suppressed FGF23 production. The association between ESA hyporesponsiveness in patients with low FGF23 levels is likely confounded. Those subjects, however, also had highest age, lowest body mass index, serum albumin and creatinine, which all indicate malnutrition. In several cross-sectional studies of haemodialysis patients, higher serum FGF23 levels were associated with lower age, higher body mass index, higher serum albumin, serum creatinine and geriatric nutritional risk index, and normalized protein catabolic index, larger abdominal muscle mass areas and creatinine production (another indicator of muscle mass).[23-25] A high-fat diet stimulated FGF23 production in mice.[26] In recent in vivo and in vitro studies involving mice and osteoblast-like cells, the effect of energy balance on FGF23 production was controlled by AMP-activated protein kinase, which works as a cellular energy sensor.[27] Haemodialysis patients usually have high FGF23 levels; therefore, low FGF23 levels may suggest constrained FGF23 production due to malnutrition. Malnutrition-inflammation complex syndrome was associated with ESA hyporesponsiveness in haemodialysis patients.[28] Hence, the additional possibility is that haemodialysis patients with malnutrition may have ESA hyporesponsiveness and also limited FGF23 production as a result of energy saving function in the bone marrow and osteocytes (Figure 2).

The association between FGF23, treatment of secondary hyperparathyroidism or anaemia, and ESA hyporesponsiveness in haemodialysis patients has been reported.[29,30] (Figure 2) Treatment of secondary hyperparathyroidism with cinacalcet reduced FGF23 levels[31] and also improved anaemia in HD patients.[32] High FGF23 levels in haemodialysis patients were associated with lower levels of ferritin and TSAT and increased usage of iron supplementation.[33] Treatment with an iron-based phosphate binder decreased FGF23 levels and improved erythropoietin responsiveness in haemodialysis patients.[34,35] On the other hand, treatment with active vitamin D in haemodialysis patients with secondary hyperparathyroidism increased FGF23 levels.[36] Vitamin D supplementation had no effect on ESA dose in vitamin D deficient haemodialysis patients.[37,38] The underlying mechanism among CKD-MBD, anaemia and ESA hyporesponsiveness is not well understood. Since FGF23 is associated with both CKD-MBD and anaemia, FGF23 may be the factor which connects them.

The mechanism of how FGF23 associates with ESA hyporesponsiveness is not well known. Erythropoiesis increased following blockade or deletion of FGF23 in previous studies.[7,8] Moreover, injection of FGF23 induced increased inflammation in mice.[39] In a study using rodents, FGF23 expression was directly induced via erythropoietin after inhibition of hypoxia inducible factor (HIF) proline hydroxylase.[40] In tumour-induced osteomalacia, HIF-1α was a direct transcriptional activator of FGF23.[41] HIF is a sensor of hypoxia and iron deficiency in cells. HIF may play a role in the association between FGF23 and anaemia. Mouse and human studies found that physiological response to iron deficiency may be

TABLE 1 Patient characteristics by initial FGF23 levels

	Overall	FGF23 quintiles, pg/mL				
		First 5–440	Second 441–1260	Third 1261–3420	Fourth 3421–8620	Fifth 8621–76 000
Number of patients	1044	208	209	209	209	209
Median FGF23, pg/mL	2001 [585, 6971]	184 [101, 297]	800 [583, 1004]	2000 [1639, 2658]	5760 [4652, 6959]	15 298 [10 536, 25 967]
Demographics						
Age, years	65.6 (12.1)	68.1 (10.9)	66.6 (11.9)	67.7 (11.1)	65.0 (12.1)	60.6 (12.8)
Male, %	61%	46%	60%	69%	64%	65%
Time with ESRD, years	8.7 (7.8)	8.5 (8.4)	8.6 (8.1)	7.5 (7.1)	8.8 (7.4)	9.8 (7.6)
Body mass index, kg/m^2	21.4 (3.6)	20.9 (3.5)	21.0 (3.7)	21.7 (3.6)	21.5 (3.0)	21.9 (3.8)
Comorbidities						
Coronary artery disease	25%	26%	23%	27%	25%	22%
Other cardiovascular disease	22%	23%	19%	23%	24%	18%
Cerebrovascular disease	12%	17%	11%	12%	11%	9%
Congestive heart failure	18%	20%	17%	16%	16%	18%
Diabetic, %	37%	43%	39%	43%	33%	29%
Hypertension, %	81%	82%	83%	86%	75%	81%
Cancer other than skin, %	10%	12%	12%	10%	8%	9%
Parathyroid Surgery, %	7%	10%	9%	6%	7%	4%
Lab measurements						
Albumin, g/dL	3.7 (0.4)	3.6 (0.4)	3.6 (0.4)	3.7 (0.3)	3.7 (0.4)	3.7 (0.4)
Creatinine, mg/dL	10.7 (2.6)	8.97 (2.55)	10.2 (2.4)	10.7 (2.3)	11.3 (2.3)	12.3 (2.4)
Albumin-corrected calcium, mg/dL	8.9 (0.7)	8.6 (0.5)	8.7 (0.6)	8.7 (0.6)	9.1 (0.7)	9.3 (0.7)
Phosphorus, mg/dL	5.3 (1.4)	4.2 (1.0)	5.0 (1.1)	5.3 (1.1)	5.7 (1.3)	6.1 (1.4)
PTH, pg/mL	162 (165)	111 (92)	144 (132)	148 (130)	156 (127)	252 (257)
25OH vitamin D, ng/mL	16.5 (6.4)	14.7 (6.4)	16.3 (6.0)	16.9 (6.1)	17.3 (6.7)	17.2 (6.4)
1,25OH vitamin D, pg/mL	13.4 (7.9)	13.1 (7.9)	13.3 (7.5)	12.8 (8.3)	14.6 (8.5)	13.2 (7.4)
Hs-CRP, mg/dL	0.08 [0.03, 0.26]	0.06 [0.03, 0.27]	0.09 [0.03, 0.27]	0.09 [0.03, 0.21]	0.09 [0.03, 0.26]	0.08 [0.03, 0.27]
Haemoglobin, g/dL	10.6 (1.1)	10.4 (1.2)	10.6 (1.2)	10.6 (1.0)	10.6 (1.1)	10.6 (1.2)
Ferritin, ng/mL	124 (220)	107 (162)	136 (317)	115 (179)	144 (275)	121 (110)
TSAT, %	25.1 (12.4)	25.8 (14.0)	24.8 (11.7)	24.2 (11.1)	26.0 (13.5)	25.1 (11.9)
Residual kidney function, %	18%	20%	19%	17%	16%	17%
Normalized PCR	0.94 (0.20)	0.89 (0.21)	0.91 (0.18)	0.95 (0.20)	0.95 (0.20)	0.98 (0.18)
White blood count, 1000 cells/mm^3	5.70 (2.02)	5.19 (2.00)	5.54 (1.96)	5.99 (2.23)	5.86 (2.02)	5.88 (1.77)
Platelets count, 1000 cells/mm^3	184 (117)	173 (92)	174 (65)	203 (177)	186 (144)	183 (59)
Treatment						
ESA type, %						
Epoetin	30%	26%	31%	30%	29%	33%
Darbepoetin	58%	64%	56%	58%	57%	53%
Pegylated epoetin beta	12%	11%	13%	12%	13%	14%
Other	0%	1%	0%	0%	1%	1%
Treatment time, min	240 (24)	242 (26)	238 (22)	240 (26)	239 (23)	240 (22)
Single-pool Kt/V	1.4 (0.3)	1.5 (0.3)	1.4 (0.3)	1.4 (0.3)	1.4 (0.3)	1.4 (0.3)
IV iron use, %	29%	27%	28%	28%	29%	36%
IV iron dose among users, mg/month	225 (145)	235 (175)	230 (126)	226 (147)	217 (132)	217 (145)

TABLE 1 (Continued)

	Overall	FGF23 quintiles, pg/mL				
		First 5–440	Second 441–1260	Third 1261–3420	Fourth 3421–8620	Fifth 8621–76 000
Oral iron use, %	6%	8%	6%	6%	4%	3%
Phosphorus binder (calcium) use, %	67%	70%	69%	68%	65%	61%
Phosphorus binder (non-calcium) use, %	52%	35%	44%	55%	60%	68%
IV vitamin D use, %	36%	21%	28%	33%	39%	56%
Oral vitamin D use, %	41%	44%	45%	44%	42%	29%
Cinacalcet use, %	24%	15%	21%	16%	31%	37%

Note: Mean (SD), median [25th, 75th percentile], or percentage are shown.
Abbreviations: Ca, calcium; ESA, erythropoietin stimulating agents; ESRD, end-stage renal disease; FGF23, fibroblast growth factor 23; hs-CRP, high sensitive C-reactive protein; IV, intravenous; PCR, protein catabolic rate; PTH, parathyroid hormone; TSAT, transferrin saturation.

TABLE 2 Distribution of variables in the outcome period by FGF 23 quintiles

	Overall	FGF23 quintiles				
		First	Second	Third	Fourth	Fifth
Number of patients	1044	208	209	209	209	209
ESA dose	5435 [3397, 8832]	5435 [4076, 9474]	5435 [3261, 8492]	5435 [3539, 8492]	5435 [3261, 8492]	4892 [3261, 8696]
Haemoglobin, g/dL	10.7 (1.0)	10.4 (1.0)	10.6 (1.0)	10.8 (0.9)	10.7 (0.9)	10.7 (1.0)
ERI	9.5 [5.7, 15.8]	11.0 [7.3, 17.6]	10.0 [5.9, 16.0]	9.3 [6.0, 15.1]	9.3 [5.3, 15.5]	8.0 [3.2, 15.2]
ESA hyporesponsiveness	13.8%	19.7%	12.9%	10.0%	11.5%	14.8%

Note: ESA dose and ERI are shown as median [25th, 75th percentile]; haemoglobin is shown as mean (SD); and ESA hypoersponsiveness is shown as percentage. Outcome period is in the 4 months following FGF23 measurement.
Abbreviations: FGF23, fibroblast growth factor 23; ERI, ESA resistance index; ESA, erythropoietin stimulating agents.

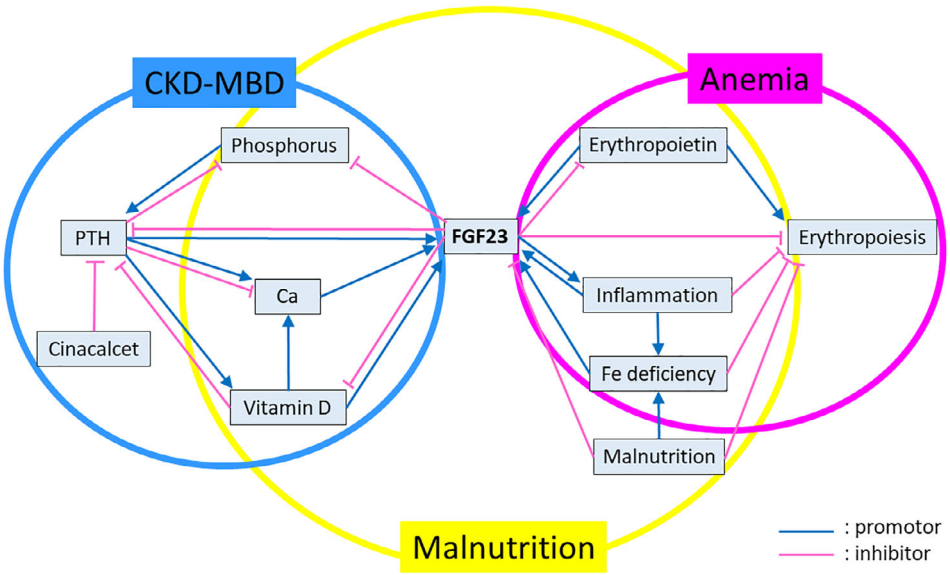

FIGURE 2 Causal diagram of the association between fibroblast growth factor 23 and anaemia in dialysis patients. The blue line indicates promotion and pink line indicates suppression. Ca, calcium; CKD-MBD, chronic kidney disease-related mineral and bone disease; Fe, iron; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone

regulating FGF23 through erythropoietin production and HIF activation.[42] Furthermore, erythropoietin-FGF23 signalling pathway was discovered to play important role in erythroid cell development and bone mineralization.[43] From these results, FGF23 may have both direct and indirect effect on erythropoiesis. Future studies are warranted to elucidate the role of FGF23 on ESA hyporesponsiveness in the context of CKD-MBD, anaemia, inflammation and malnutrition in haemodialysis patients.

Erythropoietin stimulating agent hyporesponsiveness is associated with increased mortality in haemodialysis patients.[1] In a cohort of 10 444 patients who were beginning haemodialysis treatment, higher c-terminal FGF23 levels were associated with a monotonically higher risk of mortality after multivariable adjustment.[44] High FGF23 levels may therefore partially explain the association between mortality and ESA hyporesponsiveness. Future preclinical and clinical studies are warranted to elucidate the mechanism between ESA hyporesponsiveness, FGF23 and mortality in haemodialysis patients.

In our study, little association was observed between ERI and FGF23 levels. However, ERI was strongly and linearly related to weight-adjusted EPO dose in 9386 haemodialysis patients.[45] Most of the subjects in our observational may have had a relatively stable Hb level with low variability over the 4 month outcome period. This may have made the ERI almost equivalent to weight-adjusted EPO dose. Unadjusted ERI decreased and body mass index increased with higher FGF23 quintiles in our study. Small changes in Hb level may be the reason that ERI did not work as an appropriate index for ESA hyporesponsiveness in our study.

4 | LIMITATIONS

We have several limitations in our study. First, since the study design is observational, we could not infer a causal relationship and there may be unmeasured confounders for which we could not adjust. Second, the factors which may influence anaemia such as vitamin B12 or folate are not measured. Third, comorbidities of malignancy or intestinal bleeding which may cause bleeding are not examined. Finally, the use of a 4-month outcome period during which Hb and ESA were measured may obscure the effect of FGF23 if the mechanism is through a fast-acting regulatory system.

In conclusion, compared with third quintile, both first and fifth quintiles of FGF23 levels were associated with ESA hyporesponsiveness in patients undergoing maintenance HD in Japan. Further understanding of the relationship between FGF23 and anaemia may contribute to improved management of anaemia in HD patients.

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CONFLICT OF INTEREST

T. U., T. H. and M. N. have consultancy agreements with Kyowa Kirin Co., Ltd. and have received honoraria from Kyowa Kirin Co., Ltd. N. H. has consultancy agreements with Kyowa Kirin Co., Ltd. and has received honoraria from Kyowa Kirin Co., Ltd. N. H. has also received lecture fees from Kyowa Kirin Co., Ltd., Chugai, Bayer, Ono, Kissei and Torii. H. F. and T. N. are employees of Kyowa Kirin Co., Ltd. No other conflicts of interest were disclosed.

AUTHOR CONTRIBUTIONS

T. U., J. Zh., H. F., T. N. and B. R. designed the study; J. Zh. analyzed the data; T. U. and J. Zh. made the figures; T. U., J. Zh., D. F., N. H., T. H., H. F., T. M., J. Ze., E. Y., B. R. and M. N. drafted and revised the paper; all authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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