

FGF23 and Mortality in a Large Cohort of Prevalent Hemodialysis Patients: Results from the J-DOPPS

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Background / Goal

Background

– Elevated levels of fibroblast growth factor 23 (FGF23) have been associated with mortality in the pre-dialysis and incident hemodialysis (HD) population, but few studies have examined this relationship in a large cohort of maintenance HD patients.

Goal

– We analyzed Japan Dialysis Outcomes and Practice Patterns Study (J-DOPPS) data to explore the association between FGF23 levels and all-cause mortality among maintenance HD patients.

Methods

• **Sample:** We included 1,122 maintenance HD patients from the J-DOPPS phase 5 (2012-2015) who had FGF23 measured as part of an ancillary study.

Analysis:

- **Model:** Cox proportional hazards regression, adjusted for potential confounders.
- **Outcome:** All-cause mortality rate, measured from 30 days after the first FGF23 measurement, was taken until death or departure from DOPPS.
- **Exposure:** Serum FGF23 levels were measured from the stored serum samples at 1-year intervals using a chemiluminescence immunoassay, which detects the full-length, biologically intact FGF23 molecule.
- **Adjustments:** Age, sex, years on dialysis, body-mass index (BMI), diabetes, cardiovascular (CV) disease, serum albumin, and serum creatinine.

Results

Table 1: Sample characteristics, by serum FGF23 quartile

Variable	All (n=1122)	FGF23 quartile			
		Quartile 1 (n=275)	Quartile 2 (n=285)	Quartile 3 (n=285)	Quartile 4 (n=277)
FGF23, pg/ml	2113 [583, 6880]	233 [114, 364]	1083 [829, 1583]	3947 [2910, 5295]	12411 [9322, 21618]
Age, years	65.5 (12.2)	68.0 (10.9)	66.4 (12.8)	66.3 (10.9)	61.3 (12.9)
Male, %	62.2	50.9	63.5	67.4	66.8
Dialysis vintage, years	5.8 [2.7, 12.4]	5.4 [2.2, 12.5]	5.4 [2.6, 10.1]	6.1 [2.7, 12.5]	6.9 [3.2, 13.5]
BMI, kg/m ²	21.4 (3.5)	20.9 (3.5)	21.5 (3.8)	21.5 (3.4)	21.8 (3.5)
Diabetes, %	38.9	44.0	41.1	37.5	33.2
CV disease, %	42.7	44.7	44.6	40.4	41.2
Albumin, g/dl	3.7 (0.4)	3.6 (0.4)	3.7 (0.4)	3.6 (0.4)	3.7 (0.3)
Creatinine, mg/dl	10.7 (2.8)	9.1 (2.8)	10.4 (2.6)	11.2 (2.4)	12.1 (2.7)
Corrected calcium, mg/dl	9.0 (0.7)	8.7 (0.6)	8.8 (0.6)	9.0 (0.7)	9.3 (0.7)
Phosphorus, mg/dl	5.1 (1.3)	4.1 (1.0)	4.9 (1.0)	5.3 (1.1)	6.0 (1.2)
PTH, pg/ml	116 [60, 210]	83 [44, 152]	108 [60, 189]	129 [64, 208]	180 [84, 296]
25OH vitamin D, ng/ml	16.6 (6.3)	15.0 (6.3)	16.7 (5.8)	17.3 (6.4)	17.3 (6.6)
1,25OH vitamin D, ng/ml	13.8 (8.1)	13.5 (7.9)	13.8 (8.5)	14.1 (7.8)	13.9 (8.3)
hsCRP, mg/dl	0.35 (0.90)	0.37 (0.88)	0.26 (0.55)	0.40 (1.08)	0.39 (0.99)
Calcium P binder, %	76.6	86.0	79.7	75.2	66.9
Non-calcium P binder, %	59.4	45.1	54.8	60.2	75.2
Active vitamin D, %	70.3	60.7	70.9	71.6	78.0
Cinacalcet, %	22.8	14.0	17.0	23.5	36.2

Values indicate mean (SD), median [IQR], or percentage; active vitamin D includes IV and oral forms.

Table 2: Association of serum FGF23 levels with all-cause mortality

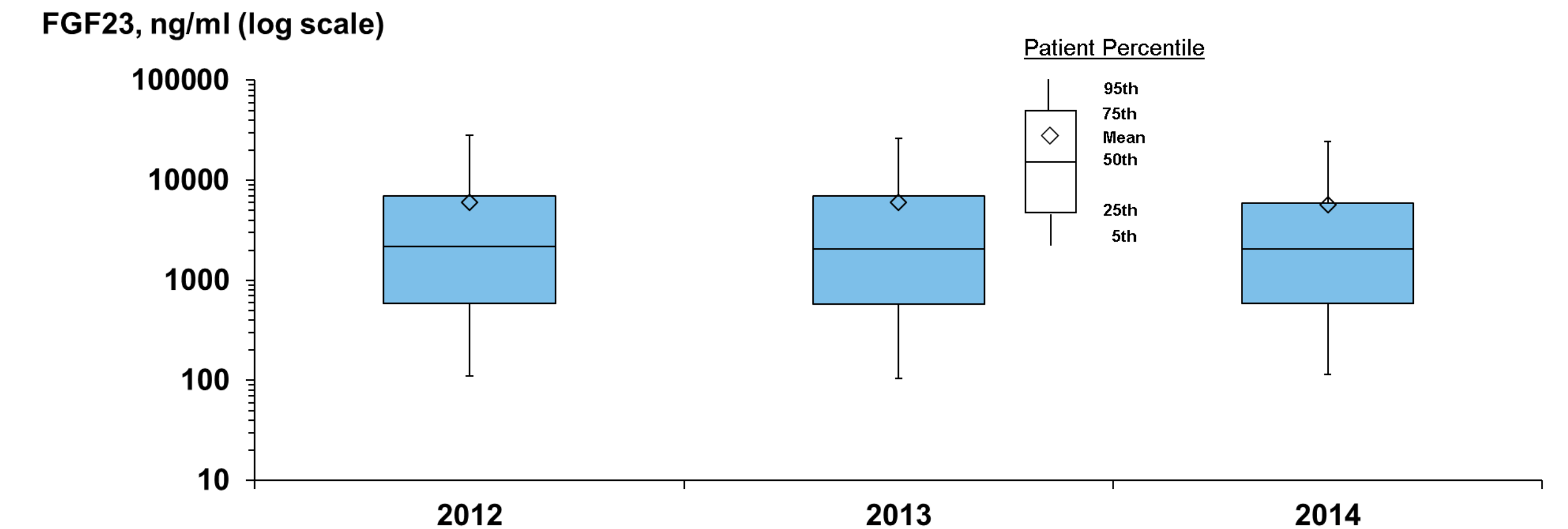
HR (95% CI)	Per 1-U increase in log FGF23	Serum FGF23 Quartile			
		Quartile 1	Quartile 2	Quartile 3	Quartile 4
No adjustment	0.95 (0.87, 1.05)	1.00 (ref)	1.25 (0.79, 1.98)	1.02 (0.68, 1.52)	0.88 (0.54, 1.41)
Model 1	1.17 (1.04, 1.32)	1.00 (ref)	1.97 (1.26, 3.08)	1.77 (1.10, 2.83)	2.45 (1.43, 4.20)
Model 2	1.18 (1.01, 1.37)	1.00 (ref)	1.99 (1.27, 3.12)	1.80 (1.07, 3.03)	2.53 (1.47, 4.34)
Model 3	1.19 (1.03, 1.38)	1.00 (ref)	2.03 (1.30, 3.17)	1.86 (1.10, 3.12)	2.61 (1.53, 4.46)

154 of the 1,122 participants died during the 3-year follow-up.
Model 1 adjusted for age, sex, dialysis vintage, BMI, diabetes, CV disease, albumin, and creatinine.
Model 2 adjusted for Model 2 covariates plus calcium, phosphorus, and PTH.
Model 3 adjusted for Model 3 covariates plus (active/analogue) vitamin D treatment.

Summary / Conclusions

- Patients with higher serum FGF23 levels tended to be younger; have longer dialysis vintage, lower prevalence of diabetes, and higher levels of serum creatinine, phosphorus, and PTH levels; and be more often prescribed non-calcium phosphate binders and PTH-lowering medications (**Table 1**).
- Among surviving patients with multiple annual measurements available (**Fig. 1**), the overall distribution of serum FGF23 levels remained remarkably stable during 2012-2014.
- In HD patients, higher levels of serum FGF23 were associated with increased mortality in adjusted analyses (**Table 2**). However, this association was less pronounced in patients with longer dialysis vintage (**Table 3**).
- **These results suggest that long-term hemodialysis patients may be less susceptible to the detrimental effects of serum FGF23, or correlated biological processes.**

Figure 1: Distribution of serum FGF23 by year, among surviving patients



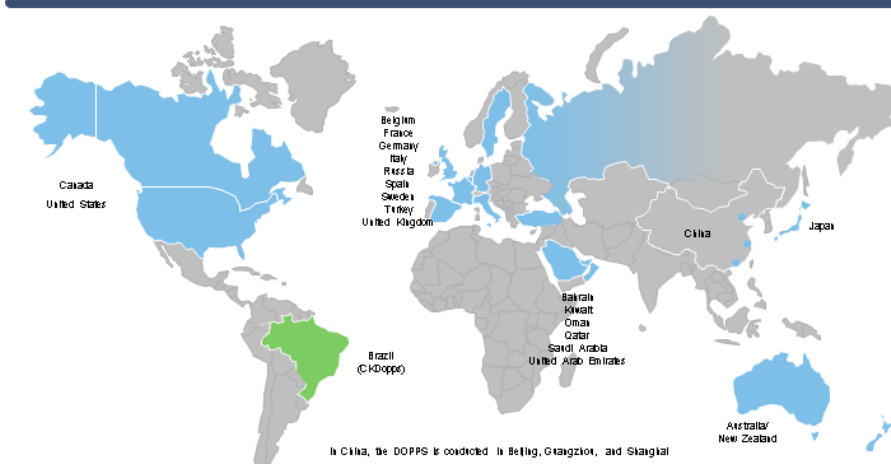
Year	Mean	FGF23 Percentile				
		5th	25th	50th	75th	95th
2012	6003	110	585	2189	6914	28091
2013	5982	105	577	2066	6962	26421
2014	5685	114	592	2051	5962	24401

N=840 patients with 3 yearly measurements during follow-up.

Table 3: Association of serum FGF23 levels with all-cause mortality, by dialysis vintage tertile

Dialysis Vintage	Median FGF23 [IQR]	HR (95% CI) per 1-U increase in log FGF23			
		No adjustment	Model 1	Model 2	Model 3
Tertile 1 (<3.5 years)	1848 [495, 5760]	1.00 (0.86, 1.17)	1.28 (1.09, 1.51)	1.29 (1.06, 1.56)	1.30 (1.07, 1.58)
Tertile 2 (3.5-9.5 years)	1977 [673, 7078]	1.01 (0.85, 1.19)	1.23 (1.00, 1.50)	1.22 (0.95, 1.57)	1.24 (0.97, 1.58)
Tertile 3 (9.5+ years)	2931 [604, 8238]	0.87 (0.72, 1.06)	1.00 (0.81, 1.25)	1.00 (0.79, 1.26)	1.01 (0.81, 1.26)
p for interaction		0.38	0.16	0.15	0.15

Model 1 adjusted for age, sex, BMI, diabetes, CV disease, albumin, and creatinine.
Model 2 adjusted for Model 2 covariates plus calcium, phosphorus, and PTH.
Model 3 adjusted for Model 3 covariates plus (active/analogue) vitamin D treatment.



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The DOPPS is an international prospective cohort study of hemodialysis treatment and patient outcomes:

- **DOPPS 1 (1996-2001):** 308 dialysis facilities and 17,034 patients in 7 countries (France, Germany, Italy, Japan, Spain, UK, and US)
- **DOPPS 2 (2002-2004), DOPPS 3 (2005-2008), DOPPS 4 (2009-2011):** ≥300 facilities and 11,000 - 13,000 patients per study phase in 12 countries (DOPPS 1 countries + Australia, Belgium, Canada, New Zealand, and Sweden)
- **DOPPS 5 (2012-2015), DOPPS 6 (2015-2017):** ~500 facilities and 30,000 patients in nine new countries (Bahrain, China, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, Russia, and Turkey) in addition to the 12 countries represented in DOPPS 4