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FGF-23 and cognitive performance in hemodialysis patients

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Abstract

Although cognitive impairment is common in hemodialysis patients, the etiology of and risk factors for its development remain unclear. Fibroblast growth factor 23 (FGF-23) levels are elevated in hemodialysis patients and are associated with increased mortality and left ventricular hypertrophy. Despite FGF-23 being found within the brain, there are no prior studies assessing whether FGF-23 levels are associated with cognitive performance. We measured FGF-23 in 263 prevalent hemodialysis patients in whom comprehensive neurocognitive testing was also performed. The cross-sectional association between patient characteristics and FGF-23 levels was assessed. Principal factor analysis was used to derive two factors from cognitive test scores, representing memory and executive function, which carried a mean of 0 and a standard deviation of 1. Multivariable linear regression adjusting for age, sex, education status, and other relevant covariates was used to explore the relationship between FGF-23 and each factor. Mean age was 63 years, 46% were women and 22% were African American. The median FGF-23 level was 3098 RU/mL. Younger age, lower prevalence of diabetes, longer dialysis vintage, and higher calcium and phosphorus were independently associated with higher FGF-23 levels. Higher FGF-23 was independently associated with a lower memory score (per doubling of FGF-23, β = −0.08 SD [95% confidence interval, CI: −0.16, −0.01]) and highest quartile vs. lowest quartile (β = −0.42 SD [−0.82, −0.02]). There was no definite association of FGF 23 with executive function when examined as a continuous variable (β = −0.03 SD [−0.10, 0.04]); however, there was a trend in the quartile analysis (β = −0.28 SD [−0.63, 0.07], P = 0.13, for 4th quartile vs. 1st quartile). FGF-23 was associated with worse performance on a composite memory score, including after adjustment for measures of mineral metabolism. High FGF-23 levels in hemodialysis patients may contribute to cognitive impairment.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Cognitive tests used in the neurocognitive battery, categorized by the primary cognitive domain evaluated.

Conflict of interest: No authors have financial conflicts related to this manuscript.

Keywords

Cognition; FGF-23; hemodialysis

INTRODUCTION

Recent studies demonstrate a high prevalence of cognitive impairment in patients with end-stage renal disease (ESRD).[1-3] Cognitive impairment adversely impacts multiple areas of patient care, including patient compliance with treatment plans, quality of life, and mortality;[3-5] therefore, understanding its pathogenesis is essential to improving outcomes for patients with ESRD. A limited number of studies have evaluated risk factors for cognitive impairment in ESRD and found that traditional cardiovascular disease (CVD) risk factors, such as blood pressure, hyperglycemia, and dyslipidemia-associated atherosclerosis, do not fully explain the high risk of cognitive impairment in this population.[6,7]

Fibroblast growth factor 23 (FGF-23) is a phosphaturic hormone, whose levels increase as kidney function declines.[8] FGF-23 is associated with multiple adverse outcomes, including left ventricular hypertrophy (LVH),[9,10] incident cardiovascular events,[11,12] and mortality in all stages of chronic kidney disease (CKD).[11,13-15] Through a Klotho-independent pathway involving stimulation of fibroblast growth factor receptors, FGF-23 may cause direct end-organ toxicity, particularly within cardiac muscle.[16] Although primarily expressed in the bone, FGF-23 is also found in high concentrations within the brain.[17,18] As both Klotho and FGF receptors are also found within the brain,[19-21] we hypothesized that high FGF-23 may have neurological effects.

There are few studies investigating factors associated with FGF-23 levels in hemodialysis patients and no studies of which we are aware that have evaluated the relationship between FGF-23 and cognitive function. We therefore evaluated both the cross-sectional relationship of patient characteristics with FGF-23 levels and the association of these levels with detailed measures of cognitive function in prevalent hemodialysis patients.

METHODS

Patients receiving chronic in-center hemodialysis at five Dialysis Clinic Inc. (DCI) units and one hospital-based unit (St. Elizabeth's Medical Center) in the greater Boston area were evaluated using previously described criteria for entry into the Cognition and Dialysis Study.[2] Reflecting the nature of the cognitive battery, eligibility criteria included English fluency as well as sufficient visual and hearing acuity to complete cognitive testing. To minimize cognitive testing floor effects and reflecting inability to provide consent, individuals with MMSE (Mini-Mental State Examination) score ≤10 and/or advanced dementia based on medical record review were excluded. Non–vascular access-related hospitalization within 1 month, delirium, receipt of hemodialysis for less than 1 month, and single pool Kt/V < 1.0 were temporary exclusion criteria. The Tufts Medical Center Institutional Review Board approved the study, which is consistent with the Declaration of Helsinki, and all participants signed informed consent forms.

Demographic, clinical, and laboratory characteristics were ascertained at the time of study enrollment. Demographic data (age, sex, and race) were obtained via participant report and review of the medical record. Education (<12th grade, high school graduate or < 2 years of college, and ≥2 years of college) and smoking history (never, current, or past smoker) were obtained via a standardized patient questionnaire. Medical history including history of CVD (a composite of either a history of coronary artery disease or peripheral vascular disease), stroke, and presence of diabetes were defined by patient history or documentation in the patient's electronic or paper charts. The cause of ESRD and time since the start of hemodialysis (dialysis vintage) were obtained from the DCI or St. Elizabeth's electronic record, as were the mean monthly predialysis systolic and diastolic blood pressures. Predialysis blood tests, including hematocrit, phosphorus, calcium, white blood cell count, C-reactive protein, albumin, and single pool Kt/V, were obtained. Vitamin D 25 hydroxy levels were measured at a later date from stored-frozen samples taken at study enrollment. All DCI laboratory tests were measured in a central laboratory in Nashville, TN.

FGF-23

A total of 263 of 314 patients recruited into the study had stored samples available for measurement of FGF-23. FGF-23 levels were measured in singlicate from plasma samples, which had been stored at −80°C, after a single freeze–thaw cycle, in batched assays at the University of Maryland School of Medicine. A C-terminal FGF-23 assay (Immutopics; Immutopics International, San Clemente, CA, USA) was used as this method has been shown previously to be highly correlated with assays of the intact FGF-23 molecule.[15] This assay has a sensitivity of 1.5 relative units per mL (RU/mL), and inter- and intra-assay coefficients of variation of less than 5%.

Cognitive assessment

Participants were administered a battery of cognitive tests by research assistants following training and direct observation by the study neuropsychologist (T. M. S.). To maintain quality and inter-rater reliability, testing was observed by the study neuropsychologist at 3- to 6-month intervals. To limit subject fatigue, all testing was completed during the first hour of hemodialysis, during which time performance appears similar to testing administered prior to start of hemodialysis.[22] The neuropsychological battery included well-validated commonly used cognitive tests that possess high inter- and intra-rater reliability. The MMSE[23] was used as a screening test and the North American Adult Reading Test served as a measure of premorbid verbal IQ.[24] The neurocognitive battery consisted of the Wechsler Memory Scale-III Word List Learning Subtest,[25] the Wechsler Adult Intelligence Scale-III Block Design and Digit Symbol-Coding Subtests,[25] and Trail Making Tests A and B[26](Trails A and B). The overall battery assesses a broad range of functioning, including global ability, supraspan learning, auditory retention, visual retention, attention/mental processing speed, visual construction/fluid reasoning, and motor speed (Supporting Information Table S1).

Principal factor analysis

To limit multiple testing as well as address collinearity between cognitive tests, principal factor analysis with varimax rotation was used as a data reduction technique.[27] As previously reported in a recent study with the same cohort of patients, we obtained two principal factors on a larger group of 292 patients.[2] The first factor was termed "memory function" and the greatest contributing tests were the Word List Learning Recall and Recognition. The second factor represented "executive functioning" or attention and processing speed as Trails A and B, Block Design, and Digit Symbol-Coding tests were the largest contributors. By definition, each standardized factor has a mean of 0 and a standard deviation of 1, with higher scores indicating better cognitive performance.

Statistical analyses

Descriptive characteristics of the study population were reported as proportions for categorical and binary variables, means with standard deviations for continuous normally distributed variables, and medians with interquartile ranges for skewed variables. To better assess differences across FGF-23 level, the study population was sorted into equally sized quartiles. Linear trends across quartiles were assessed using linear regression used for continuous variables and the Cochran–Armitage test for binary variables. Differences between categorical variables were assessed using chi-square tests.

The association of baseline characteristics with FGF-23 level was assessed using univariate and multivariable linear regression with log-transformed FGF-23 as the outcome variable in these models. The resulting β coefficients were exponentiated, yielding a geometric mean ratio for each independent variable. Percentage difference in the outcome (FGF-23) for each covariate (per standard deviation for continuous variables) was calculated by taking 1 minus the geometric mean ratio and multiplying by 100. Sex, race, history of CVD, and 25OH vitamin D were forced into the multivariable model due to previously reported associations with FGF-23,[12,15,28,29] while selection of the remaining terms was based on a $P < 0.1$ in univariate analysis.

Separate linear regression models were used to assess the relationship between both continuous FGF-23 (log base two transformed, due to a skewed distribution, representing the doubling of FGF-23 level) and FGF-23 quartiles of equal size, with the primary outcomes representing memory (factor 1) and executive function (factor 2), derived from the principal factor analysis method described earlier. Three multivariable models were constructed as follows: (1) a parsimonious model was created with adjustment for age, sex, and education; (2) an expanded model included additional adjustment for history of CVD and race, which were forced into the model based on previously reported possible associations with FGF-23,[11,15] as well as factors that demonstrated differences across quartiles of FGF-23 ($P < 0.1$); and (3) a third model additionally adjusted for calcium, phosphorus and 25OH vitamin D. Secondary analyses repeated the above multivariable analyses for each individual cognitive test. As the Trails B test is a time-limited test, a Tobit regression with censoring at 300 seconds was used.[30] As the assay to measure parathyroid hormone (PTH) changed during the study period, PTH was not included in the main analyses. However, PTH was included as a covariate in sensitivity analyses for all cognitive

tests, including the two factors. Analyses were performed using R, version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Participants with FGF-23 measured were similar to those without available samples with regard to age, sex, and race/ethnicity, but had shorter dialysis vintage and higher level of education. The mean age of study participants was 63 years, 46% were woman and 22% were African American (Table 1). The mean (SD) FGF-23 level was 5080 RU/mL (5062), with a median of 3098 RU/mL and interquartile range of 1139–7960 RU/mL. Corresponding to higher quartiles of FGF-23, there were higher calcium and phosphorus levels as well as longer dialysis vintage; age, diabetes prevalence, and 25OH vitamin D levels were all significantly lower in the higher FGF-23 quartiles.

In univariate and multivariable analyses, younger age, nondiabetic status, higher calcium, higher phosphorus, and longer dialysis vintage were all significantly associated with higher FGF-23 levels (Table 2). Calcium and phosphorus were the strongest contributors toward higher FGF-23 level, with a 1 standard deviation increase resulting in a 46% increase (95% confidence interval [CI]: [28, 66]) and 70% increase (95% CI: [49, 94]) in FGF-23 level, respectively.

When adjusted for age, sex, and education level, higher FGF-23 level was associated with worse memory function (representing the change in memory factor for each doubling of FGF-23) (β = −0.08 SD [95% CI −0.16, −0.01]) but not with executive function (Table 3). FGF-23 was also significantly associated with poorer performance on several individual tests primarily focusing on memory (short delay: −0.20 [−0.37, −0.03] and delayed recall: −0.17 [−0.34, −0.01] but also on one test of executive functioning (Trails B: 7.29 [0.26, 14.31]). The magnitude of these associations was largely preserved when adjustment was made for possible confounders, including measures of mineral metabolism.

When FGF-23 was analyzed by quartiles, individuals in the highest quartile had worse memory function in comparison with the lowest quartile (−0.42 SD [−0.82, −0.02]). Similarly, the highest quartile was associated with worse performance on several memory assessments including immediate recall total, short delayed recall, and delayed recall (−3.01 [−5.64, −0.39]; −1.32 [−2.44, −0.19] and −1.16 [−2.25, −0.06], respectively) in comparison with the lowest quartile of FGF-23 (Table 4). Significant differences between the highest and lowest quartile were also seen for tests that represent executive functioning processes, including the Digit Symbol-Coding and Trails B tests (−8.68 [−14.76, −2.59] and 48.19 [5.33, 91.06]), respectively. For the component executive function factor, although the highest three quartiles demonstrated worse scores compared with the lowest quartile, no linear trend was seen across quartiles. In sensitivity analyses in which PTH was added to the final multivariable model, similar results were seen for both the memory and the executive factors as well as for individual component tests (data not shown).

DISCUSSION

In this cohort of patients treated with maintenance hemodialysis, there was a modest association between higher serum FGF-23 levels and lower cognitive function. Specifically, our results showed that those with higher FGF-23 levels had worse performance for a composite memory factor as well as several component tests, findings that remained largely consistent after adjusting for potential confounders, including those related to mineral metabolism. Across the range of observed FGF-23 levels, which is best demonstrated in the quartile analysis, we found nearly a half standard deviation difference in cognitive performance between the lowest and highest quartiles. This magnitude is similar to the association we previously observed between CVD and executive function.[6] For the executive function factor and for the Trails B and Digit Symbol-Coding tests, we also observed lower levels of cognitive performance when comparing the 2nd through 4th quartiles to the 1st quartile. Additionally, we found several factors that were independently associated with higher FGF-23 levels, including younger age, nondiabetic status, longer dialysis vintage, and higher calcium and phosphorus levels.

To our knowledge, there are no previously published studies evaluating the relationship between FGF-23 levels and cognition. Higher FGF-23 levels are associated with multiple adverse outcomes, including LVH,[9,10] incident CVD,[11,12] progression of kidney disease,[11,14] and mortality in all stages of kidney disease,[11,13,15] although there is a debate as to whether FGF-23 is a marker of disease severity/or comorbid conditions or is in the causal pathway leading to these adverse outcomes. It is unclear whether these associations are due to the physiologic, phosphaturic effect of FGF-23 in the kidney or via a direct activation of general FGF receptors. In support of the latter, a recent animal study has demonstrated that FGF-23 directly induced LVH, a Klotho-independent effect mediated via FGF receptors within cardiac muscle.[16] These same FGF receptors are widely present throughout the brain, with subtypes expressed preferentially in distinct areas of the brain[19] and expression altered in conditions of brain injury.[31] FGF-23 is also found within brain tissue.[17] Similar to bone-derived FGF-23, the stimulus for FGF-23 production and/or the systemic effects of FGF-23 and its breakdown products (which are biologically active) in the brain remain poorly defined.[21] Klotho, the co-receptor responsible for FGF-23's action within the kidney, has also been located within the choroid plexus of the brain.[21] As Klotho's only currently known role is to allow for FGF-23 function,[32] its presence within the brain would seem to indicate an FGF-23–brain connection. It is thus possible that high levels of FGF-23 may exert neurological effects either via direct activation of FGF receptors, or in conjunction with Klotho. In support of a possible effect independent of mineral metabolism in our study, adjustment for phosphorus, calcium, and 25-OH vitamin D in our models did not diminish the association between FGF-23 and lower cognitive performance. We also note that, although the most consistent association was seen between higher FGF-23 levels and lower function on memory-related tests, we cannot be sure whether this translates into FGF having adverse effects on a particular area of the brain vs. there being limited power to detect differences with regard to executive function.

We noted that several patient-related factors, including younger age, nondiabetic status, longer dialysis vintage, and higher calcium and phosphorus levels, were associated with

higher FGF-23 levels. In a study of 219 prevalent hemodialysis patients from France, younger age, higher calcium, and higher phosphorus levels were associated with higher FGF-23 levels in univariate analysis.[13] In multivariable analysis, only phosphorus remained an independent determinant of FGF-23. This study population differed from ours in several key ways, including a longer dialysis vintage, a lower proportion of diabetic patients, and overall lower mean phosphorus levels, perhaps explaining the difference in the findings. Although the exact mechanisms remain unclear, high phosphate intake and high serum calcium are hypothesized to stimulate the release of FGF-23,[29,33] which may explain these findings. We also saw an association between longer dialysis vintage and higher FGF-23, which may be explained by a recent study which demonstrated that peritoneal dialysis patients with residual kidney function had significantly lower FGF-23 levels that those who were anuric.[34] In a similar fashion, it is likely that patients who have been dialysis dependent for a longer time have lower residual renal function and are therefore more likely to have higher FGF-23 levels. An association between diabetes and lower FGF-23 level was noted in a study of 602 patients during the earlier stages of CKD.[35] In contrast, a study of nearly 4000 patients within the CRIC cohort found higher levels of FGF-23 in diabetic CKD patients compared with nondiabetic CKD patients even after adjustment for level of kidney function.[36] It is unclear how these contrasting findings translate to dialysis patients as the mean FGF-23 level we observed in our dialysis patients was an order of magnitude higher than that of either study. Finally, the association between younger age and higher FGF-23 levels has been reported previously in both ESRD and patients during the earlier stages of CKD.[11,13] Potential explanations include a lower rate of bone turnover in older patients[37,38] (and thereby less FGF-23 secretion), lower bone mass, or lower average phosphorus intake in older patients.[39]

Our study has several limitations that need to be acknowledged when interpreting the study results. First, we did not ascertain residual kidney function and therefore could not adjust for this factor in our analyses. It has been shown that ESRD patients with higher residual function have lower FGF-23 levels[34] and these patients may have overall better functional status, which could predispose toward better cognitive function. We did, however, control for dialysis vintage in our analyses, which may serve as a proxy for residual function, partially addressing this limitation. Second, this study is cross sectional, and therefore, we are unable to determine the direction of any observed associations. Third, given the observational nature of the study, unmeasured factors and residual confounding remain possible. This may be a particular issue with FGF-23, as the factors that determine FGF-23 levels in hemodialysis patients are still being determined. In addition, some have suggested that FGF-23, as opposed to being directly pathogenic, is instead a marker of disease severity. To address this, we have attempted to include all potential measured confounders, particularly comorbidity and mineral metabolism measures.

Our study has also several strengths. First, we have detailed baseline demographic and clinical information. Additionally, we administered an array of tests which assess multiple cognitive domains and to address multiple testing associated with our chosen battery of tests, we used principal factor analysis to derive factors which we believe represent memory and executive function. Finally, although our cohort was on average more educated than the

average prevalent US hemodialysis patient, it was otherwise similar with regard to age, percent female, and prevalence of diabetes, supporting generalizability of our results.

This investigation provides data which suggest that higher FGF-23 levels are associated with poor cognitive performance. Elevated FGF-23 levels may be one of several factors predisposing hemodialysis patients to a high prevalence of cognitive impairment. Future research should attempt to replicate these findings in diverse cohorts of patients with kidney disease, as well as in longitudinal analyses. Finally, further research is required to evaluate the precise mechanism of action by which FGF-23 may affect the brain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographics and clinical characteristics stratified by quartiles of FGF-23

Variable	Full cohort N = 263	Quartile 1 N = 66	Quartile 2 N = 66	Quartile 3 N = 65	Quartile 4 N = 66	P value*
FGF-23 units (RU/mL)	3097 (1139, 7960)	134–1139	1139–3098	3098–7960	7960–15568	NA
Age (y)	63.0 (16.8)	67.1 (17.1)	65.8 (14.2)	62.6 (16.5)	56.6 (17.6)	**<0.001**
Female	46%	41%	44%	60%	39%	0.7
Black	22%	18%	23%	18%	30%	0.2
Education						0.5
>2-y college	38%	32%	38%	37%	47%	
High school – 2 y	52%	58%	56%	51%	44%	
<High school	10%	11%	6%	12%	9%	
NAART Verbal IQ	102.6 (12.3)	100.7 (13.1)	104.2 (11.2)	102.4 (11.8)	103.0 (13.2)	0.4
Diabetes	46%	56%	58%	40%	30%	**<0.001**
Hypertension	90%	86%	97%	86%	89%	0.9
PVD	22%	29%	21%	14%	24%	0.4
Stroke	17%	11%	21%	14%	23%	0.2
CAD	35%	36%	33%	35%	35%	0.9
CVD	41%	47%	38%	42%	39%	0.5
Cause of ESRD						0.08
Diabetes	33%	47%	38%	28%	20%	
Hypertension	19%	17%	15%	26%	18%	
Unknown	29%	16%	29%	26%	45%	
Glomerulonephritis	19%	20%	18%	20%	17%	
Calcium (mg/dL)	9.0 (0.7)	8.8 (0.7)	9.0 (0.8)	9.1 (0.7)	9.2 (0.7)	**0.002**
Phosphorus (mg/dL)	5.6(1.5)	4.6 (1.1)	5.3 (1.5)	6.0 (1.1)	6.3 (1.6)	**<0.001**
Vitamin D 25OH (ng/mL)	17.7 (7.7)	18.6 (9.7)	18.5 (7.1)	17.0 (6.9)	16.4 (6.7)	0.06
Hematocrit (%)	35.3 (3.6)	35.4 (3.0)	35.3 (3.4)	36.1 (3.5)	34.5 (4.3)	0.3
Albumin (g/dL)	3.8 (0.3)	3.8 (0.3)	3.7 (0.4)	3.9 (0.3)	3.8 (0.4)	0.7
Kt/V	1.51 (0.24)	1.50 (0.21)	1.46 (0.21)	1.60 (0.27)	1.49 (0.25)	0.4
Dialysis vintage (mo)	13.8 (6.4, 33.5)	7.5 (4.1, 14.5)	11.2 (4.9, 18.4)	19.7 (9.7, 35.3)	31.3 (13.0, 53.7)	**<0.001**
DBP (mmHg)	73.0 (12.2)	70.6 (11.6)	72.6 (10.4)	74.5 (11.2)	74.2 (14.9)	0.06
SBP (mmHg)	141.1 (21.0)	141.6 (16.3)	142.7 (20.3)	142.8 (20.1)	137.4 (26.1)	0.3
WBC count (K/μL)	7.4 (2.4)	7.8 (2.7)	7.2 (2.1)	7.8 (2.6)	7.0 (2.1)	0.2
CRP (mg/L)	5.3 (2.0, 11.4)	5.3 (2.5, 11.2)	6.3 (2.5, 16.6)	3.9 (1.8, 8.7)	5.6 (1.6, 14.7)	0.3
Smoking status						0.3
Current	9%	5%	14%	6%	13%	
Never	39%	36%	31%	40%	49%	
Past	52%	59%	55%	54%	38%	

Presented as mean (SD), %, or median with interquartile range as appropriate.

CAD = coronary artery disease; CRP = C-reactive protein; CVD, cardiovascular disease = composite of either CAD or PVD; FGF-23 = fibroblast growth factor 23; DBP = monthly average predialysis diastolic blood pressure; NA = not applicable; NAART = North American Adult Reading Test; PVD = peripheral vascular disease; SBP = monthly average systolic blood pressure; WBC = white blood cell.

*P value for linear trend across quartiles.

Table 2

Association between baseline patient characteristics and percent difference in FGF-23 level

	Unadjusted		Multivariable[b]	
Variable[a]	**% Difference (95% CI)**	**P value**	**% Difference (95% CI)**	**P value**
Age (y)	−33 (−43, −10)	**<0.001**	−15 (−27, −1)	**0.05**
Female	5 (−22, 43)	0.7	−13 (−37, 13)	0.3
Black	20 (−17, 73)	0.3	0 (−28, 40)	>0.9
Diabetes	**−37 (−54, −15)**	**0.002**	**−18 (−45, −5)**	**0.01**
History of CVD	5 (−30, 30)	0.8	21 (−9, 61)	0.2
Dialysis vintage (y)	**43 (23, 65)**	**<0.001**	**46 (28, 66)**	**<0.001**
Diastolic BP (mmHg)	15 (−2, 34)	0.08	−7 (−19, 9)	0.4
Calcium (mg/dL)	**27 (9, 47)**	**0.002**	**46 (28, 66)**	**<0.001**
Phosphorus (mg/dL)	**71 (49, 96)**	**<0.001**	**70 (49, 94)**	**<0.001**
Vitamin D 25OH (ng/mL)	−11 (−24,4)	0.14	−7 (−18, 6)	0.3

Bold values indicate a P value ≤0.05.

BP = blood pressure; CI = confidence interval; CVD = cardiovascular disease.

[a] All continuous variables have been standardized, the percent difference represents the change per 1 standard deviation of each relevant covariate.

[b] Adjusted for age, sex, race, diabetes, history of CVD, dialysis vintage, monthly average diastolic blood pressure, calcium, phosphorus, and vitamin.

Table 3

Cross-sectional association between doubling of FGF-23 levels and cognitive function

		Model 1		Model 2		Model 3	
Cognitive test	**Sample size**	**β (95% CI)**	**P value**	**β (95% CI)**	**P value**	**β (95% CI)**	**P value**
Factor 1 (memory)	243	**−0.06 (−0.12, −0.01)**	**0.02**	**−0.08 (−0.14, −0.01)**	**0.02**	**−0.08 (−0.16, −0.01)**	**0.05**
Factor 2 (executive)	243	−0.04 (−0.10, 0.01)	0.15	−0.02 (−0.08, 0.04)	0.5	−0.03 (−0.10, 0.04)	0.4
MMSE	263	−0.07 (−0.26, 0.11)	0.61	−0.01 (−0.20, 0.19)	0.9	0.09 (−0.14, 0.32)	0.4
Immediate recall (total)	261	−0.37 (−0.77, 0.02)	0.06	−0.38 (−0.81, 0.04)	0.08	−0.38 (−0.88, 0.13)	0.14
Short delayed recall	260	**−0.20 (−0.37, −0.03)**	**0.02**	**−0.21 (−0.39, −0.02)**	**0.03**	−0.21 (−0.42, 0.01)	0.06
Delayed recall	259	**−0.17 (−0.34, −0.01)**	**0.05**	−0.17 (−0.35, 0.01)	0.07	−0.15 (−0.36, 0.06)	0.16
Recognition	259	−0.08 (−0.27, 0.12)	0.4	−0.09 (−0.30, 0.11)	0.4	−0.11 (−0.36, 0.13)	0.4
Trail A	244	2.03 (−0.79, 4.85)	0.16	0.53 (−2.50, 3.57)	0.7	0.01 (−3.58, 3.60)	>0.9
Trail B	240	**7.29 (0.26, 14.31)**	**0.04**	7.09 (−0.34, 14.51)	0.06	**7.91 (0.75, 15.08)**	**0.03**
Digit Symbol-Coding	235	−0.47 (−1.43, 0.50)	0.3	−0.31 (−1.31, 0.69)	0.5	−1.05 (−2.23, 0.12)	0.08
Block design	257	−0.61 (−1.29, 0.06)	0.07	−0.43 (−1.12, 0.25)	0.2	−0.57 (−1.40, 0.24)	0.17

Bold values indicate a P value ≤0.05.

For each factor, β represents the change per 1 standard deviation, for cognitive tests β represents the change in test score.

For all tests except Trails A and B, a negative value indicates worse performance; for Trails A and B, a positive value indicates worse performance.

Model 1 = adjusted for age, sex, and education status.

Model 2 = Model 1 + Adjustment for race, diabetes status, history of CVD, dialysis vintage, and average pre-HD diastolic blood pressure.

Model 3 = Model 2 + Adjustment for calcium, phosphorus, and 25 hydroxy vitamin D.

MMSE = Mini-Mental State Examination.

Table 4

Association between quartiles of FGF-23 and cognitive performance[a]

Cognitive test	Quartile 1 FGF-23 from 134 to 1139	Quartile 2 FGF-23 from 1139 to 3098 β (95% CI)	Quartile 3 FGF-23 from 3098 to 7960 β (95% CI)	Quartile 4 FGF-23 from 7960 to 15568 β (95% CI)	P value for trend
Factor 1 (memory)	Ref	−0.07 (−0.38, 0.25)	−0.17 (−0.53, 0.19)	**−0.42 (−0.82, −0.02)**	**0.04**
Factor 2 (executive)	Ref	**−0.29 (−0.57, −0.02)**	**−0.32 (−0.64, −0.01)**	−0.28 (−0.63, 0.07)	0.13
MMSE	Ref	−0.37 (−1.26, 0.51)	−0.41 (−1.40, 0.59)	−0.30 (−1.42, 0.82)	0.6
Immediate recall (Total)	Ref	−1.02 (−3.09, 1.06)	−1.89 (−4.25, 0.47)	**−3.01 (−5.64, −0.39)**	**0.02**
Short delayed recall	Ref	−0.26 (−1.15, 0.62)	−0.30 (−1.30, 0.71)	**−1.32 (−2.44, −0.19)**	**0.03**
Delayed recall	Ref	−0.22 (−1.09, 0.65)	−0.59 (−1.57, 0.39)	**−1.16 (−2.25, −0.06)**	**0.04**
Recognition	Ref	−0.18 (−1.15, 0.79)	−0.70 (−1.80, 0.41)	−0.67 (−1.90, 0.56)	0.2
Trail A	Ref	7.22 (−6.94, 21.39)	11.78 (−4.33, 27.89)	4.57 (−13.49, 22.63)	0.5
Trail B	Ref	33.79 (−0.40, 67.98)	36.05 (−2.44, 74.54)	**48.19 (5.33, 91.06)**	**0.04**
Digit Symbol-Coding	Ref	**−5.21 (−10.05, −0.36)**	**−5.59 (−11.02, −0.15)**	**−8.68 (−14.76, −2.59)**	**0.01**
Block design	Ref	−1.46 (−4.69, 1.77)	−2.64 (−6.30, 1.02)	−3.64 (−7.77, 0.48)	0.08

Bold values indicate a P value <0.05 or confidence intervals that do not include 0.

β represents the mean difference between quartile 1 and each subsequent quartile. For factors 1 and 2, this represents a per standard deviation change. For all other tests, this represents the mean difference in score.

For all tests except Trails A & B, a negative value indicates worse performance; for Trails A & B, a positive value indicates worse performance.

CI = confidence interval; FGF = fibroblast growth factor 23; MMSE = Mini-Mental State Examination.

[a]Fully adjusted model including age, sex, education level, race, diabetes, history of cardiovascular disease, dialysis vintage, prehemodialysis diastolic blood pressure, calcium, phosphorus, and 25 hydroxy vitamin D.