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Association Between Chronic Kidney Disease–Mineral Bone Disease (CKD-MBD) and Cognition in Children: Chronic Kidney Disease in Children (CKiD) Study

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Rationale & Objective: Chronic kidney disease (CKD) in children is associated with cognitive dysfunction that affects school performance and quality of life. The relationship between CKD–mineral and bone disorder and cognitive function in children is unknown.

Study Design: Observational study.

Participants: 702 children enrolled in the Chronic Kidney Disease in Children (CKiD) Study.

Predictors: Plasma fibroblast growth factor 23 (FGF-23), parathyroid hormone (PTH), calcium, phosphorus, 25 hydroxyvitamin D (25[OH]D), and 1,25 dihydroxyvitamin D (1,25$[OH]_2$D).

Outcomes: Neurocognitive tests of intelligence, academic achievement, and executive functions.

Analytical Approach: Linear regression models to analyze the cross-sectional associations between log_2FGF-23, 25(OH)D, 1,25$(OH)_2$D, PTH, calcium, and phosphorus *z* scores and the cognitive test scores of interest after adjustment for demographics, blood pressure, proteinuria, and kidney function.

Results: At baseline, median age was 12 (95% CI, 8.3, 15.2) years and estimated glomerular filtration rate was 54 (40.5, 67.8) mL/min/1.73 m^2. In fully adjusted analyses, 25(OH)D, 1,25$(OH)_2$D, PTH, calcium, and phosphorus *z* scores did not associate with cognitive test scores. In fully adjusted analyses, log_2FGF-23 was associated with abnormal test scores for attention regulation ($P < 0.05$); specifically, Conners' Continuous Performance Test II Errors of Omission (β = 2.3 [1.0, 3.6]), Variability (β=1.4 [0.4, −2.4]), and Hit Reaction Time (β = 1.3 [0.2, 2.4]). Children in the highest FGF-23 tertile group had 7% and 9% greater cognitive risk for Hit Reaction Time and Errors of Omission compared with those in the lowest tertile, respectively. In fully adjusted analyses, higher FGF-23 tertile was associated with increased cognitive risk ($P < 0.05$) for Errors of Omission (β = 0.4 [0.1, 0.7]) and Hit Reaction Time (β = 0.4 [0.1, 0.7]).

Limitations: The study does not assess the cumulative effects of FGF-23 excess on cognitive function over time. Within-population stratified analyses were not performed due to limited sample size.

Conclusions: In children with CKD, higher plasma FGF-23 level is associated with lower performance in targeted tests of executive function, specifically attention regulation, independent of glomerular filtration rate.

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Chronic kidney disease (CKD) in children is associated with higher morbidity and mortality than seen in the general pediatric population.[1-3] Despite advances in the care of children with CKD, such as improved nutrition, anemia management, avoidance of aluminum-based phosphate binders, adequate dialysis, and timely kidney transplantation, emerging studies show that children with CKD remain at risk for cognitive dysfunction, particularly in the areas of attention regulation and associated executive functions.[4] Cognitive dysfunction can lead to poor school performance and lower quality of life. Lower performance has been reported in measures of academic achievement, such as numerical operations, compared with chronological age expectations.[5,6]

In prior studies of children from the Chronic Kidney Disease in Children (CKiD) cohort, median cognitive function was within the range of normal values; however, 21% to 40% of participants scored at least 1 standard deviation (SD) below the normative mean on measures of intelligence quotient (IQ), achievement, attention, and executive functions.[6,7] Similarly, in adults who had childhood-onset CKD, verbal and nonverbal IQ were lower than in their unaffected peers, and educational attainment and employment rates were lower compared with those without CKD.[8,9] In adult-onset CKD, the prevalence of severe cognitive dysfunction in patients receiving dialysis is higher than the prevalence of dementia reported in community-based populations.[10] Collectively, these studies show that children and adults with CKD are at increased risk for neurocognitive deficits that in turn can negatively affect their educational performance, disease self-management, occupational outcomes, and health-related quality of life. However, there is a paucity of literature on risk factors that increase the likelihood of cognitive dysfunction in CKD.

Fibroblast growth factor 23 (FGF-23) is a bone-derived circulating hormone that is critical for maintaining phosphorus and vitamin D homeostasis and thereby skeletal mineralization.[11-13] In CKD, plasma FGF-23 level increases early and is associated with disordered mineral metabolism,[14,15] CKD progression,[16-18] left ventricular hypertrophy,[19,20] poor cardiovascular health, and mortality.[21-24]

PLAIN-LANGUAGE SUMMARY

Cognitive impairment is a known complication of chronic kidney disease (CKD) in children. However, little is known about risk factors that might increase the likelihood of cognitive impairment in CKD. The present study provides the first large-scale evaluation of associations between biomarkers of bone and mineral metabolism and cognitive function in children with predialysis CKD. Higher plasma fibroblast growth factor 23 (FGF-23) concentrations were independently associated with poor performance on cognitive function tests, specifically measures of attention regulation. Our study is the first to provide evidence for an association between plasma FGF-23 level and complications involving the central nervous system in children with CKD.

In preclinical studies, FGF-23 was shown to directly regulate neural networks in the hippocampus, an important region for learning, memory, and attention regulation.[25] In adults with CKD, associations between circulating FGF-23 levels and neurologic complications, particularly impaired cognitive function, were examined, but the findings are controversial.[26-28] In children, FGF-23 protein is detected in the cerebrospinal fluid[29] but no prior studies have examined the relationship between levels of FGF-23 or other biomarkers of bone and mineral metabolism and cognitive function in children with and without CKD.

In the present study, we address this gap in the pediatric literature by testing the hypothesis that higher plasma FGF-23 level is associated with poor performance on specific measures of cognitive function in children with CKD. We also examine associations between other biomarkers of bone and mineral metabolism and cognitive function in this population.

METHODS

The CKiD Study is a prospective observational study that enrolled 891 children aged 1 to 16 years with estimated glomerular filtration rates (eGFRs) between 30 and 90 mL/min/1.73 m^2 at 54 centers across North America from January 2005 to March 2015.[7,30-32] The study design, methods, and exclusion criteria have been described previously.[30] The study was approved by the UCSF Institutional Review Board #18-25119, and all participants provided informed consent.

Participants

For the present cross-sectional analysis, we included 702 children aged 6 to 16 years in whom baseline measurement of plasma FGF-23, mineral metabolism biomarkers, and neurocognitive testing were performed 3 to 6 months after enrollment.

Neurocognitive Tests

A battery of tests was carefully administered to assess key areas of cognitive functions (Table S1). All tests were standardized, age normed, age appropriate, and administered to each study participant by a trained psychologist or trained technician supervised by the psychologist at each site.[7,33] We selected specific cognitive tests to: (1) align with literature pertaining to cognition in mild to moderate CKD[4-7] and (2) have strong psychometric properties that included age-based normative data. These measures include the Wechsler Abbreviated Scales of Intelligence-2 (WASI-2; intellectual function); Wechsler Individual Achievement Test-II-Abbreviated (WIAT-II-A; Total Achievement [academic achievement]); Conners' Continuous Performance Test-II (CPT-II; Errors of Omission, Errors of Commission, Hit Reaction Time, Detectability, and Variability [selective attention, impulsivity, and attention regulation]); Digit Span Backwards from the age-appropriate Wechsler Intelligence Scale (verbal working memory); parent ratings on the Behavior Rating Inventory of Executive Functions (BRIEF; executive functions) summary scores of Behavior Regulation Index (BRI), Metacognition Index, and Global Executive Composite.

Biochemistries

We measured plasma C-terminal FGF-23 using a second-generation enzyme-linked immunosorbent assay (Immutopics Int); inter- and intra-assay coefficients of variation were 11.5% and 5.7%, respectively.[15] Median plasma FGF-23 value in healthy children of comparable age was 57 (2.5th and 97.5th percentiles, 17 and 101) RU/mL. Serum vitamin D metabolites were measured using Heartland Assays as described.[15] All other biochemistry test results were determined at the CKiD Central Biochemistry Laboratory, University of Rochester.[32] Kidney function was determined by eGFR calculations using the full CKiD ($eGFR_{CKiDfull}$) equation based on serum creatinine, cystatin C, and serum urea nitrogen levels; height; and sex.[34] eGFR data were collected at all study visits compared with iohexol GFR, which was measured at select time points only. $eGFR_{CKiDfull}$ closely approximated measured iohexol GFR to describe relationships between risk factors and CKD progression in this pediatric population[35] and is the preferred equation for research purposes using this pediatric cohort.

Statistical Analysis

All analyses presented are cross-sectional, using plasma FGF-23, serum 25-hydroxyvitamin D (25[OH]D), 1,25-dihydroxyvitamin D ($1,25[OH]_2D$), parathyroid hormone (PTH), calcium, and phosphorus levels obtained at baseline as the primary exposure. Values were expressed

Table 1. Participant Characteristics in Overall CKiD Cohort and by FGF-23 Tertile

Characteristic	Overall Cohort	FGF-23 Tertile 1 (≤87.5 RU/m L)	FGF-23 Tertile 2 (87.6-147.4 RU/m L)	FGF-23 Tertile 3 (≥147.5 RU/m L)
N	702	235	233	234
Demographics				
Age, y	11.8 [8.3, 15.2]	11.5 [8.5, 15.3]	11.7 [8.3, 15.1]	12.6 [8.1, 15.2]
Female sex	270 (38%)	82 (35%)	85 (36%)	103 (44%)
White	477 (68%)	161 (69%)	161 (69%)	155 (66%)
African American	107 (15%)	29 (12%)	38 (16%)	40 (17%)
Hispanic ethnicity	94 (14%)	37 (16%)	29 (13%)	28 (12%)
Kidney				
Iohexol GFR, mL/min/1.73 m^2[a]	54 [40.5, 67.8]	64 [51.4, 76.9]	55 [45.2, 66.1]	41 [32.3, 55.4]
Glomerular CKD	223 (32%)	76 (32%)	66 (28%)	81 (35%)
Nonglomerular CKD	479 (68%)	159 (68%)	167 (72%)	153 (65%)
CKD duration, y	8.3 ± 4.9	8.0 ± 4.8	8.9 ± 4.9	8.1 ± 5.0
Laboratory				
Urine protein-creatinine ratio, mg/g[a]	0.003 [0.001, 0.009]	0.002 [0.001, 0.006]	0.002 [0.001, 0.006]	0.006 [0.002, .018]
Serum phosphorus, mg/dL[a]	4.5 ± 0.8	4.3 ± 0.7	4.4 ± 0.7	4.7 ± 0.9
Serum 25(OH)D, ng/mL	27.9 ± 11.9	28.4 ± 10.1	28.6 ± 12.0	26.8 ± 13.3
Serum 1,25(OH)$_2$D, pg/mL[a]	34.1 ± 12.7	36.5 ± 11.9	35.9 ± 12.8	29.9 ± 12.4
Serum calcium, mg/dL	9.5 ± 0.6	9.5 ± 0.5	9.5 ± 0.5	9.4 ± 0.7
Serum iPTH, pg/mL[a]	62.4 ± 72.9	40.4 ± 25.0	55.7 ± 36.9	92.4 ± 113.7
Plasma FGF-23, RU/mL	111.4 [77.8, 174.8]	67.9 [55.4, 77.9]	111.5 [98.8, 127]	223.2 [174.8, 308.2]
Medication Use				
Antihypertensive	458 (65%)	157 (67%)	146 (63%)	155 (66%)
Phosphate binders	117 (17%)	30 (13%)	30(13%)	57 (24%)
Active vitamin D	190 (27%)	30 (13%)	57 (25%)	103 (44%)

Note: Data presented as mean ± standard deviation, median [25th, 75th percentile], or number (percent).
Abbreviations: 1,25(OH)$_2$D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; CKD, chronic kidney disease; CKiD, Chronic Kidney Disease in Children; FGF-23, fibroblast growth factor 23; GFR, glomerular filtration rate; iPTH, intact parathyroid hormone.
[a]$P \leq 0.001$ by tertile.

either as a continuous or a categorical variable using tertiles. Values of FGF-23 were log2-transformed to satisfy normality assumptions. Values of phosphorus for each participant were expressed as a z score relative to age-matched values in healthy children.[36]

The primary outcome of interest was neurocognitive test performance; test values for each assessment were compared with age-appropriate norms from the general population and expressed as a standard score. Cognitive risk was defined as a standard score ≥ 1 SD below the test mean (categorical outcome). Higher cognitive test scores indicate better performance for WASI-2, WIAT-II-A, and Digit Span Backwards. Higher scores indicate worse performance for CPT-II tests, BRI, Metacognition Index, and Global Executive Composite.

We tested for differences in the distribution of each of the cognitive test standard scores across tertiles of plasma FGF-23 using the Kruskal-Wallis test and examined the unadjusted associations between cognitive test standard scores and $\log_2$ plasma FGF-23 (representing per doubling) using Pearson correlation. We also tested for differences in the prevalence of cognitive risk for each cognitive test across tertiles of FGF-23 using 2-tailed χ^2 test and examined the associations between cognitive risk and $\log_2$ FGF-23 using 1-way analysis of variance. When 1 or more cognitive function tests was associated with either $\log_2$FGF-23 or FGF-23 tertiles at a significance level < 0.1, we performed multivariable regression analyses as described next for all measures within the specific cognitive domain of interest.

We used linear regression models to examine the association between $\log_2$FGF-23, 25(OH)D, 1,25(OH)$_2$D, PTH, calcium, and phosphorus z score values and cognitive test score(s) of interest. Model 1 was unadjusted; model 2 was adjusted for sex, age, race, and Hispanic ethnicity (yes/no); model 3 was additionally adjusted for eGFR and urine protein-creatinine ratio (UPCR, yes/no ≥ 2); and model 4 was additionally adjusted for hypertension (defined as systolic blood pressure [BP] ≥ 95th percentile). In separate analyses, we used multivariable logistic regression to quantify the effect of tertiles of FGF-23 on the odds of cognitive risk; models were adjusted for the same covariates as listed. All analyses were performed using Stata 10/MP (StataCorp LP).

RESULTS

Cohort Characteristics

Characteristics of the 702 participants, overall and by tertile of plasma FGF-23, are summarized in Table 1. Median

Table 2. Neurocognitive Test Scores in CKiD Cohort

Measure	Mean	SD	Confidence Interval (5th-95th percentile)	Cognitive Risk Threshold	N	Percent at Risk
Intellectual Functioning						
WASI-2 IQ	97.2	15.7	71-122	≤85	590	23%
Academic Achievement						
WIAT II-A Total Achievement	95.6	18.1	65-126	≤85	289	29%
Attention Regulation						
CPT-II Omission	52.8	14.4	42-81	≥60	537	18%
CPT-II Commission	51.6	11.0	33-66	≥60	538	26%
CPT-II VAR	51.1	11.2	35-69	≥60	538	25%
CPT-II HIT REACT	49.0	12.0	32-73	≥60	538	17%
CPT-II DETECT	52.0	10.3	33-65	≥60	538	23%
Executive Functioning						
Digit Span Backward	9.2	2.9	4-13	≤7	269	27%
BRIEF-P BRI	52.9	11.7	38-76	≥60	585	26%
MI	55.0	11.6	38-76	≥60	582	32%
GEC	54.4	11.7	38-76	≥60	662	31%

Note: Cognitive risk is defined as scores ≥ 1 SD below expected performance for age. Mean and SD of normative values for cognitive test scores provided the basis for establishing a risk category. IQ calculated from WASI-2: mean ± SD, 100 ± 15 (higher scores are better), ACHIEVE; achievement total scaled score derived from Word Reading, Numerical Operations, and Spelling from WIAT-II-A: mean ± SD, 100 ± 15 (higher scores are better), CPT-II scores depending on age: COMMISSION, HIT REACT, OMISSION, VAR, DETECT: mean ± SD, 50 ± 10 (higher scores are worse), Digits Span Backwards is a subset of Digit Span from the age-appropriate Wechsler Intelligence Scale for Children-IV Test: mean ± SD, 19 ± 3, higher scores are better. BRIEF-P all scores: BRI, MI, and GEC: mean ± SD, 50 ± 10 (higher scores are worse for BRI, MI, and GEC).

Abbreviations: BRI, Behavior Regulation Index scaled score from BRIEF; BRIEF-P, Behavior Rating Inventory of Executive Functions, parents rating; CKiD, Chronic Kidney Disease in Children; COMMISSION, Commission T Score; CPT-II, Conners' Continuous Performance Test-II; DETECT, Detectability; GEC, Global Executive Composite scaled score from BRIEF derived from BRI and MI; HIT REACT, Hit Reaction time; IQ, intelligence quotient; MI, Metacognition Index scaled score from BRIEF; OMISSION, Omission T Score; SD, standard deviation; VAR, Variability; WASI-2, Wechsler Abbreviated Scales of Intelligence-2; WIAT-II-A, Wechsler Individual Achievement Test-II-Abbreviated.

age was 12 years, 38% were female, 68% were white, and 15% were African American, with 14% reporting Hispanic ethnicity. Median eGFR was 54.2 (interquartile range, 40-68) mL/min/1.73 m^2. CKD was caused by nonglomerular disease in 68% of participants, 65% reported taking antihypertensive medications, 27% took active vitamin D sterols, and 17% took phosphate binders. Median plasma FGF-23 concentration was 111 (interquartile range, 78-175) RU/mL. Compared with the lowest FGF-23 tertile (≤87.5 RU/mL), participants in the highest tertile (≥147.5 RU/mL) had lower eGFRs and were more likely to have higher UPCR, phosphorus, and PTH values and lower $1,25(OH)_2D$ concentrations (Table 1).

Measures of Cognitive Function and Cognitive Risk Assessment

As a group, children with CKD performed near the expected cognitive score for their age (Table 2). WASI-2 IQ score (mean ± SD, 97.2 ± 15.6) was in the normal range. WIAT-II-A Total Achievement score (mean ± SD, 95.6 ± 18.1) also was within the normal range. Mean values for measures of attention regulation (ie, CPT-II Errors of Omission, Errors of Commission, Hit Reaction Time, Detectability, and Variability) were age appropriate. Parental ratings of executive functions revealed few overall problems, with the 3 major BRIEF indexes (BRI, Metacognition Index, and Global Executive Composite) reflecting age-appropriate functioning.

We then determined the percentage of children with CKD who were at cognitive risk (Table 2). When analyzed as a group, cognitive test scores in children with CKD were within the normal range. However, when individual patients were examined, a large percentage (18%-33%) of children were categorized as being at risk for cognitive dysfunction (ie, ≥1 SD below the test mean) for a given cognitive test. Specifically, the percentage of children at cognitive risk was 23% for IQ, 29% for total achievement, 18% to 26% for attention regulation, and 26 to 33% on parent ratings of executive functioning. Compared with the distribution in otherwise healthy children (ie, ∼16%), these data demonstrate that a greater percentage than expected of children with mild to moderate CKD are at risk for cognitive dysfunction.

Associations of FGF-23 Concentrations With Cognitive Test Scores

Unadjusted associations between plasma FGF-23 levels and cognitive test scores are shown in Table S2. Among the cognitive domains examined, scores for the following tests showed associations ($P < 0.1$) by either FGF-23 tertile, $\log_2$FGF-23, or both: CPT-II tests for Errors of Omissions, a measure of selective attention; Variability and Hit Reaction Time, measures of attention regulation; Detectability, a measure of overall attention; and WIAT II-A Total Achievement score.

Table 3. Adjusted Associations Between FGF-23 Level and Cognitive Tests for Attention Regulation

Cognitive Function Tests	Association With log_2FGF-23		Association With FGF-23 Tertile 2 vs 1		Association With FGF-23 Tertile 3 vs 1	
	Coefficient (β) (95% CI)	*P*	Coefficient (β) (95% CI)	*P*	Coefficient (β) (95% CI)	*P*
CPT-II Omissions	2.3 (1.0 to 3.6)	0.001[a]	−0.2 (−3.2 to 2.7)	0.9	5.8 (2.6 to 9.0)	<0.001[a]
CPT-II Commissions	0.1 (−0.9 to 1.2)	0.8	1.3 (−1.1 to 3.7)	0.3	−0.3 (−2.9 to 2.3)	0.8
CPT-II VAR	1.4 (0.4 to 2.4)	0.009[a]	0.3 (−2.1 to 2.6)	0.8	3.0 (0.5 to 5.5)	0.02[a]
CPT-II HIT REACT	1.3 (0.2 to 2.4)	0.02[a]	−1.0 (−3.5 to 1.5)	0.4	4.8 (2.1 to 7.5)	0.001[a]
CPT-II DETECT	0.7 (−0.2 to 1.7)	0.1	0.6 (−1.7 to 2.8)	0.5	1.5 (−0.9 to 3.9)	0.2

Note: Plasma FGF-23 concentrations were either log base 2 transformed (representing doubling of FGF-23) or expressed as tertiles (β coefficient and *P* for highest vs lowest tertile). Outcome of interest is CPT-II scores depending on age: OMISSION. COMMISSION, VAR, HIT REACT, and DETECT. Coefficient represents β value of FGF-23 effect after accounting for all other variables in the model. Covariates: age, sex, race, Hispanic, estimated glomerular filtration rate, urine protein-creatinine ratio ≥ 2, and hypertension (≥95th percentile systolic blood pressure). N = 490 for CPT-II OMISSIONS, N = 491 for CPT-II Commissions, VAR, HITREACT, and DETECT.

Abbreviations: CI, confidence interval of T score; COMMISSION, Commission T Score; CPT-II, Conners' Continuous Performance Test-II; DETECT, Detectability; FGF-23, fibroblast growth factor 23; HIT REACT, Hit Reaction time; OMISSION, Omission T Score; VAR, Variability.

[a]Statistically significant.

Multivariable Regression Analysis of Associations of FGF-23 With Cognitive Function

The association between log_2FGF-23 and FGF-23 tertile for cognitive test scores showing an unadjusted association ($P < 0.1$) with FGF-23 level was further examined using multivariable linear regression; the fully adjusted model included age, sex, race, eGFR, UPCR, and systolic hypertension (Tables 3, S2, and S3). We observed that log2 FGF-23 level remained significantly associated with poorer scores for 3 of the 5 measures of attention regulation, specifically CPT-II Errors of Omission, Variability, and Hit Reaction Time in the fully adjusted model (Table 3). Interestingly, the strength of the association between plasma FGF-23 level and CPT-II Errors of Omission, Variability, and Hit Reaction Time was stronger in model 4 compared with models 2 and 3 after adjusting for eGFR, UPCR, and hypertension (Table S3). Among the covariates, younger age was associated with lower performance for CPT-II Errors of Omission, Variability, and Hit Reaction Time and nonwhite race was associated with poor performance for CPT-II Errors of Omission. CPT-II Detectability, CPT-II Errors of Commission, and WIAT II-A scores were not associated with FGF-23 levels in fully adjusted analyses. The associations between plasma FGF-23 levels and test scores for CPT-II Errors of Omission, Variability, and Hit Reaction Time were also significant in the fully adjusted model when plasma FGF-23 level was expressed as tertiles (Table 3).

Relationship Between FGF-23 Concentrations and Cognitive Risk

The prevalence of cognitive risk for each cognitive test according to FGF-23 tertiles is shown in Table 4. In the unadjusted analysis, cognitive risk showed associations ($P < 0.1$) either by FGF-23 tertile or log_2FGF-23 or both with the following tests: WASI-2 IQ, CPT-II Errors of Omission and Hit Reaction Time, and the BRIEF BRI summary score. In the fully adjusted model, higher FGF-23 tertile was significantly associated with increased cognitive risk for 2 of the 5 measures of attention regulation (CPT-II Errors of Omission and Hit Reaction Time; Tables 4 and S4). Compared with children with FGF-23 levels ≤ 87.5 RU/mL, children with FGF-23 levels ≥ 147.5 RU/mL had 9% (26% vs 17%) and 6% (22% vs 16%) higher rates of cognitive risk on CPT-II Errors of Omission and Hit Reaction Time, respectively. In pairwise comparisons for these 2 cognitive measures, there is a statistically significant difference between tertiles 2 and 3 ($P < 0.01$) but not between tertiles 1 and 2. WASI-2 IQ, a measure of intellectual functioning, and summary scores from the BRIEF test, measures of executive function, were not associated with FGF-23 levels in fully adjusted analyses. The associations between plasma FGF-23 levels and cognitive risk for CPT-II Errors of Omission were also significant in the fully adjusted model when expressed as FGF-23 level doubling (Table 4).

Relationship Between Mineral Metabolites and Cognitive Function

To assess the specificity of the association of FGF-23 levels with cognitive dysfunction, we examined whether levels of other markers of mineral metabolism were associated with differences in cognitive test performance in children with CKD. In the fully adjusted analyses, 25(OH)D, $1,25(OH)_2D$, PTH, calcium, and phosphorus z scores did not associate with any of the cognitive test scores listed in Table 2. There was a trend toward significance for associations between phosphorus z scores and CPT-II Errors of Omission ($P = 0.08$) and between serum 25(OH)D levels and CPT-II Errors of Commission ($P = 0.06$) in the fully adjusted analyses.

DISCUSSION

In the present cohort of 702 children with predialysis CKD, higher plasma FGF-23 levels were independently

Table 4. Adjusted Associations Between FGF-23 Levels and Cognitive Risk for Attention Regulation

Cognitive Function Tests	Association With log_2FGF-23		Association With FGF-23 Tertile 2 vs 1		Association With FGF-23 Tertile 3 vs 1	
	Coefficient (β) (95% CI)	*P*	Coefficient (β) (95% CI)	*P*	Coefficient (β) (95% CI)	*P*
CPT-II Omissions	0.4 (0.1 to 0.6)	0.002[a]	−0.06 (−0.2 to 0.8)	0.8	0.8 (0.2 to 1.4)	0.01[a]
CPT-II Commissions	−0.09 (−0.3 to −0.1)	0.5	0.03 (−0.5 to 0.5)	0.9	−0.2 (−0.7 to 0.4)	0.5
CPT-II VAR	0.2 (−0.03 to 0.4)	0.08	−0.2 (−0.7 to 0.3)	0.4	0.4 (−0.2 to 0.9)	0.2
CPT-II HIT REACT	0.2 (−0.07 to 0.4)	0.2	0.03 (−0.6 to 0.6)	0.9	0.8 (0.2 to 1.5)	0.008[a]
CPT-II DETECT	0.1 (−0.08 to 0.4)	0.2	0.2 (−0.4 to 0.7)	0.7	0.4 (−0.2 to 0.9)	0.2

Note: Plasma FGF-23 concentrations were either log base 2 transformed (representing doubling of FGF-23) or expressed as tertiles (β coefficient and *P* for highest vs lowest tertile). Outcome of interest is cognitive risk defined as a score > 1 standard deviation below age-specific mean on the CPT-II scores depending on age: OMISSION, COMMISSION, VAR, HIT REACT, and DETECT. Coefficient represents β value of FGF-23 effect after accounting for all other variables in the model. Covariates: age, sex, race, Hispanic, estimated glomerular filtration rate, urine protein-creatinine ratio ≥ 2, and hypertension (≥95th percentile systolic blood pressure). N = 490 for CPT-II Omissions, N = 491 for CPT-II Commissions, VAR, HITREACT and DETECT.
Abbreviations: CI, confidence interval of *z* score; COMMISSION, Commission T Score; CPT-II, Conners' Continuous Performance Test-II; DETECT, Detectability; FGF-23, fibroblast growth factor 23; HIT REACT, Hit Reaction time; OMISSION, Omission T Score; VAR, Variability.
[a]Statistically significant.

associated with poor performance in 3 of the 5 cognitive tests for selective attention and attention regulation. Risk for poor performance (defined as ≥1 SD below test mean) on CPT-II Errors of Omission was 1.5 times greater in participants with FGF-23 levels ≥ 147.5 RU/mL compared with those with FGF-23 levels ≤ 87.5 RU/mL. We also observed a significant association between log_2FGF-23 and FGF-23 tertiles with other measures of attention, specifically CPT-II Hit Reaction Time and Variability, but not for CPT-II Errors of Commission and Detectability. The associations remained significant after adjustment for known risk factors for cognitive dysfunction, including eGFR, systolic BP, and proteinuria.[4] More importantly, these associations were specific for FGF-23 levels because no association was found for levels of other markers of CKD–mineral and bone disorders, including vitamin D metabolites, PTH, calcium, and phosphorus.

In a child with CKD, cognitive deficits can have a major adverse effect over their lifetime on educational achievement, disease self-management, occupational outcome, and health-related quality of life.[8-10] The substantial improvements in the care of CKD realized over the last 4 decades are predicted to be neuroprotective. However, emerging studies show that some children with CKD remain at risk for cognitive dysfunction.[4-7,37] The present study provides the first large-scale evaluation of associations between CKD–mineral and bone disorders and cognitive function. As a group, children with mild to moderate CKD in our study tested within age-appropriate norms for IQ, academic achievement, and attention/executive functions. However, when individual patients were examined, a substantial proportion of children were at risk for cognitive dysfunction; the prevalence of risk ranged from ∼18% to 33% for any given cognitive test. These findings were consistent with prior reports.[4]

In our prior study, we observed that GFR and proteinuria were associated with poor performance on some but not all of the neurocognitive tests examined.[7] Specifically, iohexol-based GFR was a significant predictor of academic achievement skills, with each 10 mL/min/1.73 m^2 increase in iohexol-based GFR being associated with a 1.4-point increase in achievement skills, but not with any of the other cognitive tests examined. Proteinuria was a significant predictor for poor performance on Verbal IQ and Full-Scale IQ, but not for Performance IQ, and for poor performance on CPT-II Errors of Omission, but not for Errors of Commission.[7] These findings suggest that there may be a particular threshold for kidney disease burden before one can observe cognitive dysfunction in a specific domain, and the adverse effects of early CKD on cognition can only be delineated with more precise measurements of the respective cognitive domains (intelligence, achievement, attention dimension, and executive functions).

There is emerging evidence that hypertension adversely affects cognitive function in children with and without CKD.[38] Children with early life primary hypertension performed poorly on cognitive tests, particularly in the domains of attention, working memory, and executive function. Learning disability is several-fold higher in children with hypertension compared with children with prehypertension, suggesting that there is a real-world impact of poor neurocognitive test performance in youth with primary hypertension.[39] In the CKiD cohort, children with elevated systolic and diastolic BPs had worse scores on the WASI compared with normotensive children.[33] Participants with systolic visit-to-visit BP variability in the upper tertile scored lower on the Delis-Kaplan Executive Function System Verbal Category Switching test compared with participants with BP variability in the lower tertile, suggesting that the difficulties with executive function may be related in part to increased visit-to-visit BP variability.[31] In our regression models, we adjusted for elevated systolic BP (Tables 3 and 4) and diastolic BP, but neither covariate alone or in combination attenuated the associations between plasma FGF-23 levels and cognitive test performance, suggesting that mechanisms by which FGF-23 levels affect cognition are independent of blood pressure.

Moreover, unlike FGF-23, elevated BP was not associated with CPT-II cognitive tests in the CKiD cohort.

Observations from CKiD were corroborated in a recent meta-analysis that assessed cognitive and educational outcomes in children with CKD.[40] In that analysis, cognitive deficits were more prevalent than in the general population; the specific patterns of deficit were evident for attention, memory, and executive function domains. Regarding attention regulation, children with CKD showed problems with attention regulation when assessed using CPT-II Errors of Omission and Commission tests.[40] In the present study, we found that level of FGF-23, a marker of disordered bone and mineral metabolism, is a strong independent predictor of poor attention regulation, with plasma FGF-23 levels ≥ 147.5 RU/mL associated with 50% greater risk for poor attention regulation in children with mild to moderate CKD.

To our knowledge, to date our study is the first to examine the associations between FGF-23 levels and cognitive function using a targeted array of neurocognitive tests in a large representative cohort of children with CKD. In adults with CKD, whether FGF-23 level associates with cognitive function is unclear.[26-28] Further, risk factors for cognitive dysfunction in children may be distinctly different from those in adults, thus limiting comparisons. In 2 studies of adult patients with and without CKD, no association between FGF-23 level and incident cognitive dysfunction was observed.[26,28] However, cognitive testing was limited to telephone interviews, and direct assessment of cognitive function was not performed. In contrast, in a smaller cohort of adults receiving dialysis, high plasma FGF-23 concentrations associated with memory deficits when individuals were assessed using a detailed battery of neurocognitive tests.[27] In our study, we found statistically significant relationships between higher FGF-23 levels and poor selective attention and attention regulation more generally—functions that can be strongly associated with working memory and short-term recall.

Whether FGF-23 contributes directly or indirectly to biological mechanisms underlying impaired cognitive function in children with CKD remains to be determined. There is a paucity of literature on the actions of FGF-23 in the central nervous system. FGF-23 has been detected in cerebrospinal fluid in humans and in rodent brain.[25,29,41] In vitro cultures of murine hippocampal cells demonstrate that FGF-23 modulates neuron morphology and synaptic density,[25] potentially making such functions as attention and memory vulnerable to FGF-23 excess. However, the biological effect of such regulation of hippocampal neural networks by FGF-23 is yet to be investigated. Of interest, the role of the hippocampus in attention regulation was recently investigated; magnetic resonance imaging performed in a large cohort of children with attention deficit-hyperactivity disorder showed reduced brain volumes in the amygdala, hippocampus, and other areas known to control attention-related behavior.[42] The present study demonstrated that high FGF-23 concentrations in children with CKD associate with poor attention regulation, findings that support the hypothesis that FGF-23 has an important biological role in the central nervous system.

Our study has some limitations. First, we did not measure serum klotho in our cohort. Klotho is a cofactor for renal actions of FGF-23 to inhibit phosphate transport and $1,25(OH)_2D$ synthesis.[43] Higher soluble klotho concentrations were recently shown to associate with better cognitive function in preclinical studies and in the aging population.[44] Currently, reliable assays to measure klotho in children with CKD are not available and normal reference ranges in children are not well established. Second, further studies are needed to determine whether FGF-23 level associates with cognitive dysfunction in CKD in other population cohorts and to assess the effects of cumulative FGF-23 excess on cognitive function over time. Should our findings be replicated in both cross-sectional and longitudinal investigations, this would suggest that higher FGF-23 level is a biological marker for cognitive dysfunction in children.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: List of cognitive function tests

Table S2: Neurocognitive test scores by FGF-23 tertiles and unadjusted association with log_2FGF-23

Table S3: Neurocognitive test scores and adjusted associations between FGF-23 and cognitive tests for attention regulation, all models

Table S4: Proportion of children at cognitive risk according to FGF-23 tertile and unadjusted association with log_2FGF-23

Table S5: Adjusted associations between FGF-23 and cognitive risk for attention regulation, all models

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