Anemia, Iron Deficiency and FGF23 in CKiD Study

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Background

- Fibroblast growth factor 23 (FGF23) is an important bone-derived hormone implicated in the pathogenesis of chronic kidney disease-mineral bone disorder (CKD-MBD), CKD progression, and CKD-associated cardiovascular morbidity.
- Anemia-related factors, specifically Iron deficiency and erythropoietin (EPO), have been demonstrated to increase FGF23 production, among other stimulators (including mineral-related factors such as phosphate).
- Anemia, which is also common in CKD, has been associated with increased morbidity and mortality, increased risk of cardiovascular disease and decreased quality of life in children with CKD.
- Both absolute and functional iron deficiency anemia are fundamental complications in CKD patients.

Aims

- To determine how iron deficiency and anemia associate with FGF23 levels in a pediatric CKD patient cohort.

Methods

- In the largest national pediatric CKD cohort (the Chronic Kidney Disease in Children (CKiD) Study), anemia, iron and FGF23 profiles were characterized in a cross-sectional analysis.
- Participants included children aged 1 month to 16 years old with mild to moderate CKD.
- Using Pearson correlation coefficients (for normally distributed data) or Spearman rank correlation coefficients (for non-normally distributed data), associations were assessed among iron parameters (serum iron, TSAT, ferritin, hepcidin), hematologic parameters (hemoglobin SDS, MCV, and/or RDW), renal/mineral metabolism parameters (eGFR, albumin-corrected calcium, and/or phosphate SDS), and FGF23 levels.
- Multivariable linear regression model was used to evaluate associations between hematologic/iron parameters and FGF23.

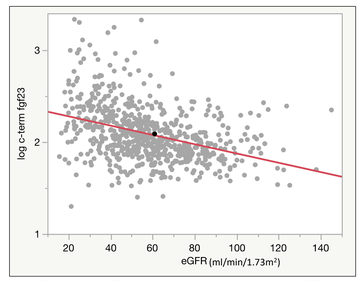
Results

- In a cross-sectional analysis of 686 pediatric CKD patients (median (interquartile range) age 11 (8, 15) years, 62% male, 14% Hispanic), the median estimated glomerular filtration rate (eGFR) was 55 (41.1, 71.4) ml/min/1.73m^2, and the median age-related hemoglobin standard deviation score (SDS) was -1.1 (-2.3, 0.2).
- Anemic subjects had higher FGF23 concentration than non-anemic subjects (153 vs 103 RU/mL, p<0.0001) (**Table 1**).
- In bivariate analyses, log-transformed FGF23 levels were inversely associated with hemoglobin SDS, serum iron, eGFR, and serum calcium, and were positively associated with age-related phosphate SDS **(Figure 2).**
- In a multivariable linear regression model, log-transformed FGF23 was inversely associated with serum iron, independent of age, sex, race, eGFR, and phosphate SDS (β= -0.0008, p=0.048); however this relationship was not significant when additionally adjusted for hemoglobin SDS and calcium. Log-transformed FGF23 remained inversely associated with hemoglobin SDS, independent of age, sex, race, eGFR, phosphate SDS, calcium, and serum iron (β= -0.02, p=0.023).

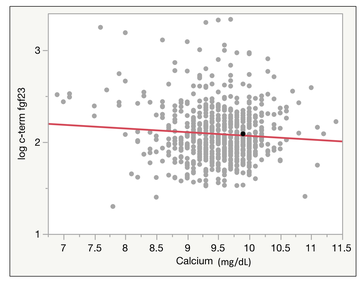
Table 1: Characteristics of anemic vs non-anemic participants at baseline

	Anemia (N=181)	No Anemia (N=505)	p-value
Age (years)	13 (10, 15)	11 (7,14)	<0.001
Male	99 (54.7%)	322 (63.8%)	0.03
Race			0.0003
Caucasian	110 (60.8%)	356 (70.5%)	
African-American	40 (22.1%)	65 (12.9%)	
American Indian	4(2.2%)	7(1.4%)	
Native Hawaiian	2(1.1%)	0	
Asian	5(2.8%)	11(2.2%)	
Other	13(7.2%)	15(2.9%)	
More than one race (excluding AA)	3(1.7%)	23(4.5%)	
More than one race (including AA)	4(2.2%)	28(5.5%)	
Hispanic	33 (18.2%)	60 (11.9%)	0.042
CKD duration (years)	8 (3,13)	8 (4,11)	0.97
Cause of CKD			<0.0001
Nonglomerular	98 (54.1%)	367 (72.7%)	
Glomerular	83 (45.9%)	138 (27.3%)	
C-terminal FGF23 (RU/mL)	153.1 (98.3, 248.9)	102.7 (73.8, 153.3)	<0.0001
Intact FGF23 (RU/mL)	78.6 (56.9, 128.7)	67.1 (50.2, 96.7)	0.0414
Serum Creatinine (mg/dL)	1.4 (1.08, 1.95)	1 (0.73, 1.3)	<0.0001
eGFR (ml/min/1.73m2)	42.7 (30.5, 55.7)	59.3 (45.2, 75.4)	<0.0001
Height adjusted z-score	−0.63 (-1.68, 0.115)	−0.45 (-1.27, 0.38)	<0.0392
Weight adjusted z-score	0.05 (-0.85, 1.09)	0.09 (-0.77, 0.99)	0.81
Albumin (g/dL)	4.2 (3.9, 4.4)	4.4 (4.2, 4.6)	<0.0001
Calcium (mg/dL)	9.3 (9.0, 9.7)	9.6 (9.3, 9.9)	<0.0001
Phosphate (mg/dL)	4.4 (3.9, 5.1)	4.4 (4, 4.8)	0.67
Phosphate SDS	−0.67 (-1.67, 0.17)	−1 (-1.67, -0.33)	0.0054
Hemoglobin (g/dL)	11.1 (10.2, 11.6)	13.1 (12.4, 14.1)	<0.0001
Hemoglobin SDS	−3.2 (-4, -2.4)	−0.4 (-1.3, 0.75)	<0.0001
MCV (fL)	84 (80, 87)	83.2 (80, 86.3)	0.2496
RCD (%)	13.4 (12.8, 14.5)	13.1 (12.6, 13.6)	<0.0001
Serum Iron (μg/dL)	64 (44.75, 80)	74 (56, 100)	0.0086
TSAT (%)	22 (16.5, 27.5)	24 (16, 32)	0.2533
Ferritin	62 (38, 146)	40 (26, 63.5)	0.0003
Absolute Iron Deficiency	22 (34.92)	81 (33.61%)	0.88
Functional Iron Deficiency	3 (4.84%)	2 (0.82%)	0.0589
Iron Deficiency	25 (40.32%)	83 (34.44%)	0.4574
ESA use	33 (18.23%)	30 (5.94%)	<0.0001
Iron supplementation	71 (39.23%)	109 (21.58%)	<0.0001

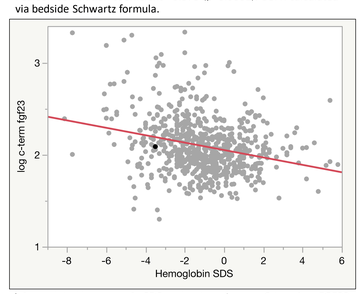
Figure 1: Bivariate analyses of hematologic, iron, renal/mineral-related parameters vs. log-transformed C-terminal FGF23



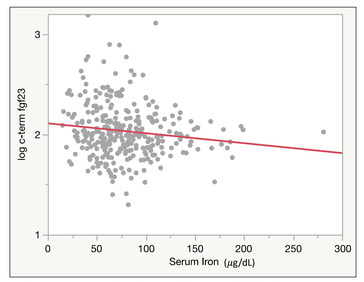
a) eGFR (ml/min/1.73m^2) vs. log-transformed C-terminal FGF23. Pearson correlation coefficient=-0.375 (p<0.0001). eGFR calculated via bedside Schwartz formula.



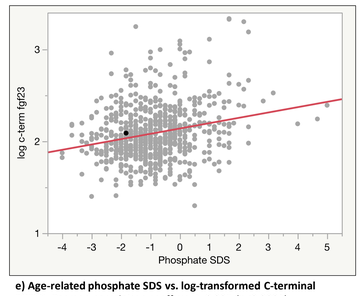
b) Calcium vs. log-transformed C-terminal FGF23. Pearson correlation coefficient=-0.076 (p=0.046).



c) Age-related hemoglobin SDS vs. log-transformed C-terminal FGF23. Pearson correlation coefficient=-0.266 (p<0.0001).



d) Serum iron vs. log-transformed C-terminal FGF23. Pearson correlation coefficient=-0.135 (p=0.017).



e) Age-related phosphate SDS vs. log-transformed C-terminal FGF23. Pearson correlation coefficient=0.235 (p<0.0001).

Conclusions

- Decreased hemoglobin levels are independently associated with increased FGF23 levels in pediatric CKD.
- Treatment of anemia and iron deficiency may lower FGF23 levels, and therefore may potentially slow CKD progression and decrease CKD-associated cardiovascular morbidity.

Future Steps:

- Future analyses will assess relationships among longitudinal changes in hemoglobin SDS, iron parameters and FGF23.

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